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(71) Applicant *(for all designated States except US)*: **ASTEX TECHNOLOGY LIMITED** [GB/GB]; 436 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0QA (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VUILLARD, Laurent, Michel, Marie** [FR/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0QA (GB). **PATEL, Sahil, Joe** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0QA (GB). **YON, Jeffrey, Roland** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0QA (GB). **CLEASBY, Anne** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0QA (GB). **HAMILTON, Bruce, John** [GB/GB]; 5 West Road, Histon, Cambridge, Cambridgeshire CB4 9LH (GB). **SHAH, Aleem** [GB/GB]; 33b Victoria Street, Littleport, Ely, Cambridgeshire CB6 1LU (GB).

(74) Agents: **BRASNETT, Adrian, H.** et al.; Mewburn Ellis, York House, 23 Kingsway, London, Greater London WC2B 6HP (GB).

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(54) Title: CRYSTAL STRUCTURE OF BETA SITE APP CLEAVING ENZYME (BACE) AND METHODS OF USE THEREOF

(57) Abstract: The present application discloses and claims mutant BACE proteins, recombinant BACE proteins, processes for crystallizing BACE and in particular to its crystal structure and to the uses of this structure in drug discovery.

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Crystal Structure Of Beta Site App Cleaving Enzyme (Bace) And Methods Of Use Thereof

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Field of the Invention

The present invention relates to the mutant BACE proteins, recombinant BACE proteins, processes for crystallizing BACE and in particular to its crystal structure and to the uses of this structure in drug discovery.

Background to the Invention

Alzheimer's disease

Alzheimer's disease (AD) is estimated to afflict more than 20 million people worldwide and is believed to be the most common form of dementia. Alzheimer's disease is a progressive dementia in which massive deposits of aggregated protein breakdown products – amyloid plaques and neurofibrillary tangles accumulate in the brain. The amyloid plaques are thought to be responsible for the mental decline seen in Alzheimer's patients.

Aβ or amyloid-β-protein is the major constituent of the plaques which are characteristic of Alzheimer's disease (De Strooper et al, 1999). Aβ is a 39-42 residue peptide formed by the specific cleavage of a class I transmembrane protein called APP, or amyloid precursor protein. A β-secretase activity cleaves this protein between residues Met671 and Asp672 (numbering of 770aa isoform of APP) to form the N-terminus of Aβ. A second cleavage of the peptide is associated with β-secretase to form the C-terminus of the Aβ peptide.

Beta Site APP Cleaving Enzyme (BACE) and Alzheimer's Disease

Several groups have identified and isolated aspartate proteases that have β-secretase activity (Hussain et al., 1999; Lin et. al, 2000; Yan et. al, 1999; Sinha et. al., 1999 and Vassar et. al., 1999). β-secretase is also known in the literature as Asp2 (Yan et. al, 1999), Beta site APP Cleaving Enzyme (BACE or BACE1) (Vassar et. al., 1999) or memapsin-2 (Lin et al., 2000). BACE was identified using a number of experimental approaches such as EST database analysis (Hussain et al. 1999); expression cloning (Vassar et al. 1999); identification of human homologs from public databases of predicted *C. elegans* proteins (Yan et al. 1999) and finally utilizing an inhibitor to purify the protein from human brain (Sinha et al. 1999). Thus, five groups employing three different experimental approaches led to the identification of the same enzyme, making a strong case that BACE is a β-secretase. Mention is also made of the patent literature: WO96/40885, EP871720, U.S. Patents Nos. 5,942,400 and 5,744,346, EP855444, US 6,319,689, WO99/64587, WO99/31236, EP1037977, WO00/17369, WO01/23533, WO0047618, WO00/58479, WO00/69262, WO01/00663, WO01/00665, US 6,313,268.

BACE is a membrane bound type 1 protein that is synthesized as a partially active proenzyme, and is abundantly expressed in brain tissue. It is thought to represent the major β-secretase activity, and is considered to be the rate-limiting step in the production of Aβ. It is thus of special interest in the pathology of Alzheimer's disease, and in the development of drugs as a treatment for Alzheimer's disease.

BACE was found to be a pepsin-like aspartyl proteinase, the mature enzyme consisting of the N-terminal catalytic domain, a transmembrane domain, and a small cytoplasmic domain. BACE has an optimum activity at pH 4.0-5.0 (Vassar et al, 1999) and is inhibited weakly by standard pepsin inhibitors such as pepstatin. It has been shown that the catalytic domain minus the transmembrane and cytoplasmic domain has activity against substrate peptides (Lin et al, 2000). Consequently, this soluble catalytic domain is suitable for crystallization studies and a crystal structure of this will give a representative structure of the BACE active site for the design of inhibitor molecules.

The likelihood of developing Alzheimer's disease increases with age, and as the aging population of the developed world increases, this disease becomes a greater and greater problem. In addition to this, there is a familial link to Alzheimer's disease and consequently

any individuals possessing the double mutation of APP known as the Swedish mutation (in which the mutated APP forms a considerably improved substrate for BACE) have a much greater chance of developing AD, and also of developing it at an early age (*see also* US 6,245,964 and US 5,877,399 pertaining to transgenic rodents comprising APP-Swedish). Consequently there is a strong case for developing a compound that can be used in a prophylactic fashion for these individuals.

Hence, drugs that reduce or block BACE activity would reduce Aβ levels and levels of fragments of Aβ in the brain or elsewhere where Aβ or fragments thereof deposit and thus slow the formation of amyloid plaques and the progression of AD or other maladies involving deposition of Aβ or fragments thereof (Yankner, 1996; De Strooper and Konig, 1999). BACE is therefore an important candidate for the development of drugs as a treatment against Alzheimer's disease and/or against such other maladies.

The therapeutic potential of inhibiting the deposition of Aβ has motivated many groups to isolate and characterize secretase enzymes and to identify their potential inhibitors (*see, e.g.*, WO01/23533 A2, EP0855444, WO00/17369, WO00/58479, WO00/47618, WO00/77030, WO01/00665, WO01/00663, WO01/29563, WO02/25276, US5,942,400, US6,245,884, US6,221,667, US6,211,235, WO02/02505, WO02/02506, WO02/02512, WO02/02518, WO02/02520, WO02/14264).

The gene encoding APP is found on chromosome 21, which is also the chromosome found as an extra copy in Downs syndrome. Downs syndrome patients tend to acquire Alzheimers disease at an early age, with almost all those over 40 years of age showing Alzheimers-type pathology (Oyama et al., 1994). This is thought to be due to the extra copy of the APP gene found in these patients, which leads to overexpression of APP and therefore to increased levels of APPβ causing the high prevalence of Alzheimers disease seen in this population. Thus inhibitors of BACE could be useful in reducing Alzheimers-type pathology in Down's syndrome patients.

It would therefore be useful to inhibit the deposition of Aβ and portions thereof by inhibiting BACE through inhibitors designed from the BACE structure as provided herein. The determination of the three-dimensional structure of BACE provides a basis for the design of new and specific ligands for BACE. For example, knowing the three-dimensional structure of BACE, computer modelling programs may be used to design different

molecules expected to interact with possible or confirmed binding cavities or other structural or functional features of BACE or structure-based design approaches may used such as those described in Blundell *et al* (Nature Reviews, Drug Discovery, Vol 1, pg 45-54, 2002).

Ideally it would be desirable to have an abundant supply of this enzyme in homogenous form. It would also be preferable to solve the structure of a form of BACE with an unoccupied active site. This could be used to soak in small molecule inhibitors of the enzyme and to investigate their binding modes. We describe here the high yielding production of BACE from bacterial cells in homogenous form, and the generation of protein suitable for crystallisation and structure determination of BACE in Apo form

Protein Crystallisation

It is well known in the art of protein chemistry that crystallising a protein is an uncertain and difficult process without any clear expectation of success. It is now evident that protein crystallization is the main hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of the protein crystallographer's laboratory. There are many references, which describe the difficulties associated with growing protein crystals (Kierzek AM. and Zielenkiewicz P. (2001) Biophysical Chemistry 91 1-20 *Models of protein crystal growth;* Wiencek JM (1999) Annu Rev Biomed Eng 1 505-534 *New Strategies for crystal growth*).

The reasons why it is commonly held that crystallization of protein molecules from solution is the major obstacle in the process of determining protein structures are many; proteins are complex molecules, and the delicate balance involving specific and non-specific interactions with other protein molecules and small molecules in solution, is difficult to predict.

Each protein crystallizes under a unique set of conditions, which cannot be predicted in advance. Simply supersaturating the protein to bring it out of solution will not work, the result would, in most cases, be an amorphous precipitate. Many precipitating agents are used, common ones are different salts, and polyethylene glycols, but others are known. In addition, additives such as metals and detergents can be added to modulate the behaviour of the protein in solution. Many kits are available (e.g., from Hampton Research), which attempt to cover as many parameters in crystallization space as possible, but in many cases

these are just a starting point to optimize crystalline precipitates and crystals which are unsuitable for diffraction analysis. Successful crystallization is aided by knowledge of the proteins behaviour in terms of solubility, dependence on metal ions for correct folding or activity, interactions with other molecules and any other information that is available. Even so, crystallization of proteins is often regarded as a time-consuming process, whereby subsequent experiments build on observations of past trials.

In cases where protein crystals are obtained, these are not necessarily always suitable for diffraction analysis; they may be limited in resolution, and it may subsequently be difficult to improve them to the point at which they will diffract to the resolution required for analysis. Limited resolution in a crystal can be due to several things. It may be due to intrinsic mobility of the protein within the crystal; this can be difficult to overcome, even with other crystal forms. It may be due to high solvent content within the crystal, which consequently results in weak scattering. Alternatively, it could be due to defects within the crystal lattice, which means that the diffracted x-rays will not be completely in phase from unit to unit within the lattice. Any one of these or a combination of these could mean that the crystals are not suitable for structure determination.

Some proteins never crystallize, and after a reasonable attempt it is necessary to examine the protein itself and consider whether it is possible to make individual domains, different N or C-terminal truncations, or point mutations. It is often hard to predict how a protein could be re-engineered in such a manner as to improve crystallisability. Sometimes the inclusion of a ligand in the crystallisation mixture is essential for the production suitable crystals. Our understanding of crystallisation mechanisms is still incomplete and the factors of protein structure, which are involved in crystallisation, are not well known.

BACE Production for Crystallisation

Beta secretase (BACE) is an integral membrane protein containing a signal sequence, a pro-peptide, a catalytic aspartyl protease domain, a transmembrane region and a C-terminal cytoplasmic region. During transit through the endoplasmic reticulum, Golgi apparatus and trans Golgi network the pro-peptide is cleaved by a furin-like protease (Bennett et al 2000, Creemers et al 2001) and N-glycosylation is added and matured (Haniu et al 2000). The protein contains 4 potential N-linked glycosylation sites, all of which are used (Bennett et al, 2000).

Certain active recombinant BACEs - different from those of the herein invention - have been produced using heterologous expression systems for mammalian cells (Vassar et al, 1999, Hussain et al, 1999), insect cells (Mallender et al, 2001) and bacterial cells (Lin et al 2000). Preferred constructs for crystallisation would be soluble and lack glycosylation: the former can be achieved by C-terminal truncation of the protein to remove the transmembrane and cytoplasmic regions; while glycosylation could be removed either by use of a deglycosylating agent such as PNGase F, by expression of the protein in bacteria or by mutation of the glycosylation sites.

The protein used for BACE crystallisation by Hong et al (2000) was produced in bacteria and was truncated at the C-terminus. Their protein was produced as insoluble inclusion bodies and required refolding to give soluble, active protein. Refolding of BACE is made more complex by the presence of 3 disulphide bonds in the native protease domain, which require careful control of redox conditions to form during *in-vitro* refolding. The protein produced by Hong et al was a mixture of products and was crystallised with inhibitor bound (see WO 01/00663, WO 01/00665, and US 6,545,127).

Mention is also made of WO 02/25276, which describes the crystallisation of BACE produced in mammalian cells. The protein produced also was a mixture of protein species and was also crystallized with an inhibitor bound.

Mention is also made of WO03/012089, which describes the crystallisation of BACE produced from insect cells. The co-ordinates of BACE with an inhibitor bound are provided.

Summary of the Invention

In general aspects, the present invention is concerned with the provision of a new, high resolution, apo, crystal form of BACE and the use of this structure in identifying or obtaining agent compounds (especially inhibitors of BACE) for modulating BACE activity, and in preferred embodiments identifying or obtaining actual agent compounds/inhibitors. Crystal structure information presented herein is useful in designing potential inhibitors and modelling them or their potential interaction with the BACE binding cavity. Potential inhibitors may be brought into contact with BACE to test for ability to interact with the BACE binding cavity. Actual inhibitors may be identified from among potential inhibitors synthesized following design and model work performed *in silico*. An inhibitor identified

using the present invention may be formulated into a composition, for instance a composition comprising a pharmaceutically acceptable excipient, and may be used in the manufacture of a medicament for use in a method of treatment.

Thus, according to a first aspect of the present invention there is provided a mutant BACE protein, which protein lacks one or more proteolytic cleavage sites recognized by clostripain (or another protease which recognizes the same cleavage site as clostripain). In particular, the protein is a BACE protein, which comprises the sequence set out in residues 45 to 455 of SEQ ID NO:2 (43 to 453 SwissProt P56817), or a fragment thereof comprising residues corresponding to 58 to 398 of SEQ ID NO:2, modified by the following changes: (a) substitution or deletion of at least one residue which is a proteolytic cleavage site recognised by clostripain; and (b) optionally the replacement of from 1 to 30 other amino acids by an equivalent or fewer number of amino acids. It will be understood that when the BACE protein comprises a fragment as defined above, the fragment will comprise at least feature (a) and optionally feature (b).

The modification is such that the BACE protein preferably retains at least one proteolytic cleavage site recognised by clostripain so that it may be cleaved to provide homogeneous location at which cleavage occurs.

According to a second aspect of the present invention there is provided a mutant BACE protein which is truncated at the N-terminal up to and including R42, R45, G55, R56 or R57. In a preferred aspect, when the protein is truncated up and including R56 the residue at position 57 is not arginine. It may for example be lysine.

In a third aspect the invention provides a mutant BACE protein selected from: (a) SEQ ID 6; (b) SEQ ID 8; (c) SEQ ID 10; (d) SEQ ID 12; (e) SEQ ID 14; (f) SEQ ID 16; (g) SEQ ID 18; (h) SEQ ID 19; (i) SEQ ID 20; (j) SEQ ID 21.

In another aspect, the invention contemplates a nucleic acid (e.g. DNA or RNA) sequence encoding the BACE protein of the invention, as well as the complementary nucleic acid sequence counterpart.

The nucleic acids of the invention may be isolated, or may be present in the context of a vector or host cell. Thus, in another aspect, the invention contemplates a vector comprising the nucleic acid of the invention.

The nature of the vector of the invention is not critical to the invention. Any suitable vector may be used, including expression vectors, plasmid, virus, bacteriophage, transposon, minichromosome, liposome or mechanical carrier.

The expression vectors of the invention are DNA constructs suitable for expressing DNA which encodes the desired peptide and which may include: (a) a regulatory element (e.g. a promoter, operator, activator, repressor and/or enhancer), (b) a structural or coding sequence which is transcribed into mRNA and (c) appropriate transcription, translation, initiation and termination sequences. They may also contain sequence encoding any of various tags (e.g. to facilitate subsequent purification of the expressed protein, such as affinity (e.g. His tags).

Particularly preferred are vectors which comprise an expression element or elements operably linked to the DNA of the invention to provide for expression thereof at suitable levels. Any of a wide variety of expression elements may be used, and the expression element or elements may for example be selected from promoters, enhancers, ribosome binding sites, operators and activating sequences. Such expression elements may comprise an enhancer, and for example may be regulatable, for example being inducible (via the addition of an inducer).

The vector may further comprise a positive selectable marker and/or a negative selectable marker. The use of a positive selectable marker facilitates the selection and/or identification of cells containing the vector.

In another aspect, the invention contemplates a host cell comprising the vector of the invention. The nucleic acid of the invention may be intrdoduced into the host cell by any of a large number of convenient methods, including calcium phosphate transfection, DEAE-Dextran mediated transfection, electroporation or any other method known in the art.

Any suitable host cell may be used, including prokaryotic host cells (such as *Escherichia coli*, *Streptomyces* spp. and *Bacillus subtilis*) and eukaryotic host cells. Suitable eukaryotic host cells include insect cells (e.g. using the baculovirus expression system), mammalian cells, fungal (e.g. yeast) cells and plant cells. Preferred mammalian cells are animal cells such as CHO, COS, C 127, 3T3, HeLa, HEK 293, NIH 3T3, BHK and Bowes melanoma (particularly preferred being CHO-K1, COS7, Y1 adrenal and carcinoma cells).

Cell-free translation systems can also be used to produce the peptides of the invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989).

Prokaryotic host cells are preferred in circumstances where the BACE protein is required in an unglycosylated state.

According to another aspect of the invention there is provided a process for producing the BACE protein of the invention comprising the steps of: (a) culturing the host cell of the invention under conditions suitable for expression of the BACE protein; and optionally (b) isolating the expressed recombinant BACE protein.

In a further aspect the invention provides a method of making BACE protein which comprises proteolytically cleaving a BACE protein which lacks one of more proteolytic cleavage sites as described above, the cleavage desirably occurring at (and including) one of position 42, 45, 55, 56 or 57, preferably 42, 56 or 57. Clostripain, or another protease which recognises the same cleavage site as clostripain, may be used.

Thus the resulting BACE protein of this aspect of invention will be a protein whose N-terminal corresponds to 45, 48, 58, 59 or 60 of SEQ ID NO:2, and whose C-terminal region extends to and includes at least 398 of SEQ ID NO:2. Preferably the C-terminal region terminates at a residue between a point corresponding to and including 398 up to and including 455. This BACE protein may additionally comprise a C-terminal tag, such as a tag comprising from 5 to 15 residues, such as a his tag or the like.

In another aspect of the invention there is provided a process for producing refolded recombinant BACE protein comprising the steps of: (a) solubilising the recombinant BACE; (b) diluting the solubilised BACE into an aqueous buffer containing sulfobetaine (for example at a concentration of 10 to 50 mM, for example 10 mM); and (c) maintaining the diluted solution at low temperature (for example, 3 to 6°C) and at high pH (e.g. 9 to 10.5) for at least 2 weeks (typically 3 weeks, more typically 4 weeks).

In another aspect the invention provides a process for producing a crystal of BACE comprising the step of growing the crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME (for example, 20-24 % PEG 5000 MME, e.g. 20-22.5 %

PEG 5000 MME), 180-220 mM (e.g. 200 mM) ammonium iodide and 180-22- mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6). In a further aspect the reservoir buffer may additionally comprise from 0 to 5% (v/v) glycerol, for example 2.5% v/v.

In another aspect the invention provides various BACE crystals, including a crystal of BACE having a hexagonal space group $P6_122$ (and optionally having unit cell dimensions of a=b=103.2 Å, c=169.1 Å, $\alpha=\beta=60°$, $\gamma=120°$, and a unit cell variability of 5% in all dimensions); a crystal of BACE having a resolution better than 3 Å (for example, better than 2.5 Å, e.g. better than 1.8 Å), and a crystal of BACE comprising a structure defined by all or a portion of the co-ordinates of Table 1.

In another aspect the invention provides a three-dimensional representation of BACE or of a portion of BACE, which representation comprises all or a portion of the coordinates of Table 1. The representation is preferably a BACE model.

The invention also contemplates a three-dimensional representation of a compound which fits the BACE model of the invention.

The invention also contemplates a computer-based method for the analysis of the interaction of a molecular structure with a BACE structure of the invention, which comprises: (a) providing a BACE model; (b) providing a molecular structure to be fitted to said BACE model; and (c) fitting the molecular structure to the BACE model to produce a compound model.

In another aspect the invention provides a computer-based method for the analysis of the interaction of a molecular structure with a BACE structure of the invention, which comprises: (a) providing the structure of a BACE as defined by the coordinates of Table 1; (b) providing a molecular structure to be fitted to said BACE structure; and (c) fitting the molecular structure to the BACE structure of Table 1.

In another aspect the invention provides a computer-based method for the analysis of molecular structures which comprises: (a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ("selected coordinates"); (b) providing the structure of a molecular structure to be fitted to the selected coordinates; and (c) fitting the structure to the selected coordinates of the BACE structure.

In another aspect the invention provides a computer-based method of rational drug design comprising comprising: (a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ("selected coordinates"); (b) providing the structures of a plurality of molecular fragments; (c) fitting the structure of each of the molecular fragments to the selected coordinates; and (d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

In another aspect the invention provides a method for identifying a candidate modulator (e.g. candidate inhibitor) of BACE comprising the steps of: (a) employing a three-dimensional structure of BACE, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one BACE binding cavity, the three-dimensional structure being defined by atomic coordinate data according to Table 1; and (b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

In another aspect the invention provides a method for identifying an agent compound (e.g. an inhibitor) which modulates BACE activity, comprising the steps of: (a) employing three-dimensional atomic coordinate data according to Table 1 to characterise at least one (e.g. a plurality of) BACE binding site(s); (b) providing the structure of a candidate agent compound; (c) fitting the candidate agent compound to the binding sites; and (d) selecting the candidate agent compound.

In another aspect the invention provides a method of assessing the ability of a candidate modulator to interact with BACE which comprises the steps of: (a) obtaining or synthesising said candidate modulator; (b) forming a crystallized complex of BACE and said candidate modulator; and (c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said candidate modulator to interact with BACE.

In another aspect the invention provides a method for determining the structure of a compound bound to BACE, said method comprising: (a) mixing BACE with the compound to form a BACE-compound complex; (b) crystallizing the BACE-compound complex; and (c) determining the structure of said BACE-compound(s) complex by reference to the data of Table 1.

In another aspect the invention provides a method for determining the structure of a compound bound to BACE, said method comprising: (a) providing a crystal of BACE; (b)

soaking the crystal with one or more compound(s) to form a complex; and (c) determining the structure of the complex by employing the data of Table 1.

In another aspect the invention provides a method of determining the three dimensional structure of a BACE homologue or analogue of unknown structure, the method comprising the steps of: (a) aligning a representation of an amino acid sequence of the BACE homologue or analogue with the amino acid sequence of the BACE of Table 1 to match homologous regions of the amino acid sequences; (b) modelling the structure of the matched homologous regions of said target BACE of unknown structure on the corresponding regions of the BACE structure as defined by Table 1; and (c) determining a conformation for the BACE homologue or analogue which substantially preserves the structure of said matched homologous regions.

In another aspect the invention provides a method of providing data for generating structures and/or performing rational drug design for BACE, BACE homologues or analogues, complexes of BACE with a potential modulator, or complexes of BACE homologues or analogues with potential modulators, the method comprising: (i) establishing communication with a remote device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE, at least one sub-domain of the three-dimensional structure of BACE, or the coordinates of a plurality of atoms of BACE; (b) structure factor data for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE homologue or analogue generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and (ii) receiving said computer-readable data from said remote device.

In another aspect the invention provides a computer system containing one or more of: (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a target BACE protein generated

by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

In another aspect the invention provides a computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion of the structure coordinates of BACE of Table 1, or a homologue of BACE, wherein said homologue comprises backbone atoms that have a root mean square deviation from the Cα or backbone atoms (nitrogen-carbon$_\alpha$-carbon) of Table 1 of less than 2.0 Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å and most preferably less than 0.5 Å when superimposed on the coordinates provided in Table 1 for the residue backbone atoms.

In another aspect the invention provides a computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for BACE according to Table 1; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

In another aspect the invention provides a computer readable medium with at least one of: (a) atomic coordinate data according to Table 1 recorded thereon, said data defining the three-dimensional structure of BACE, or at least selected coordinates thereof; (b) structure factor data for BACE recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a BACE-ligand complex or a BACE homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

In another aspect the invention provides a method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1, and either (a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said

protein or (b) assigning NMR spectra Peaks of said protein by manipulating the coordinates of Table 1.

In another aspect the invention contemplates BACE modulator molecules, medicaments, pharmaceutical compositions and drugs obtainable by, or obtained by, the processes and methods of the invention, and to methods of therapy (e.g. the treatment of Alzheimer's disease) using such products.

It is to be understood that, except where explicitly stated otherwise, references herein to "BACE protein" or "BACE peptide", "mutant BACE protein" or "mutant BACE peptide" and to "BACE protein" or "BACE peptide", as well as references to any of the foregoing which are further defined *inter alia* by reference to one or more specific amino acid sequences, are intended to cover BACE homologues, allelic forms, species variants, derivatives and muteins thereof (as defined below).

Thus, references to mutant BACE proteins having particular amino acid sequences may optionally be interpreted to cover the corresponding homologues, allelic forms, species variants, derivatives and muteins (as defined below) of that particular BACE amino acid sequence.

Definitions

Where used herein and unless specifically indicated otherwise, the following terms are intended to have the following meanings in addition to any broader (or narrower) meanings the terms might enjoy in the art:

The term "isolated" is used herein to indicate that the isolated moiety (e.g. peptide or nucleic acid) exists in a physical milieu distinct from that in which it occurs in nature. For example, the isolated peptide may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs. The absolute level of purity is not critical, and those skilled in the art can readily determine appropriate levels of purity according to the use to which the peptide is to be put. The term "isolating" when used a step in a process is to be interpreted accordingly.

In many circumstances, the isolated moiety will form part of a composition (for example a more or less crude extract containing many other molecules and substances), buffer system,

matrix or excipient, which may for example contain other components (including proteins, such as albumin).

In other circumstances, the isolated moiety may be purified to essential homogeneity, for example as determined by PAGE or column chromatography (for example HPLC or mass spectrometry). In preferred embodiments, the isolated peptide or nucleic acid of the invention is essentially the sole peptide or nucleic acid in a given composition.

The proteins and nucleic acids of the invention need not be isolated in the sense defined above, however. For example, more or less crude culture supernatants (e.g. "spent" medium) may contain sufficient concentrations of the proteins or nucleic acids of the invention for use in several applications. Preferably, such supernatants are fractionated and/or extracted, but in many circumstances they may be used without pretreatment. They are preferably derived from spent media used to culture the host cells of the invention (for example, the bacterial sources described infra). The supernatants are preferably sterile. They may be treated in various ways, for example by concentration, filtration, centrifugation, spray drying, dialysis and/or lyophilisation. Conveniently, the culture supernatants are simply centrifuged to remove cells/cell debris and filtered.

The term “pharmaceutical composition” is used herein to define a solid or liquid composition in a form, concentration and level of purity suitable for administration to a patient (e.g. a human or animal patient) upon which administration it can elicit the desired physiological changes.

The term “recombinant” as applied to the proteins of the invention is used herein to define a protein that has been produced by that body of techniques collectively known as "recombinant DNA technology" (for example, using the nucleic acid, vectors and or host cells described herein).

The term “synthetic” as applied to the peptides of the invention is used herein to define a peptide that has been chemically synthesised *in vitro* (for example by any of the commercially available solid-phase peptide-synthesis systems).

As used herein in relation to the vectors of the invention, the term "operably linked" refers to a condition in which portions of a linear nucleic acid sequence are capable of influencing the activity of other portions of the same linear nucleic acid sequence. For example, DNA

for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; a ribosome binding site is operably linked to a coding sequence if it is positioned in the correct reading-frame so as to permit translation.

By "apo-structure" we mean the three-dimensional structure of the protein that contains no ligand, e.g. substrate or product or cofactor or inhibitor i.e. the active site of the protein is empty.

In the following by "binding site" or "binding cavity" we mean a site (such as an atom, a functional group of an amino acid residue or a plurality of such atoms and/or groups) in a BACE binding cavity, which may bind to an agent compound such as a candidate inhibitor. Depending on the particular molecule in the cavity, sites may exhibit attractive or repulsive binding interactions, brought about by charge, steric considerations and the like.

Binding sites are sites within a macromolecule, or on its surface, at which ligands can bind. Examples are the catalytic or active site of an enzyme (the site on an enzyme at which the amino acid residues involved in catalysing the enzymatic reaction are located), allosteric binding sites (ligand binding sites distinct from the catalytic site, but which can modulate enzymatic activity upon ligand binding), cofactor binding sites (sites involved in binding/co-ordinating cofactors e.g. metal ions), or substrate binding sites (the ligand binding sites on a protein at which the substrates for the enzymatic reaction bind). There are also sites of protein-protein interaction.

In the following by "active site" we mean a site (such as an atom, a functional group of an amino acid residue or a plurality of such atoms and/or groups) in a BACE binding cavity, which is involved in catalysis.

By "fitting", is meant determining by automatic, or semi-automatic means, interactions between one or more atoms of a candidate molecule and at least one atom of a BACE structure of the invention, and calculating the extent to which such interactions are stable. Interactions include attraction and repulsion, brought about by charge, steric considerations and the like. Various computer-based methods for fitting are described further herein.

By "root mean square deviation" we mean the square root of the arithmetic mean of the squares of the deviations from the mean.

By a "computer system" we mean the hardware means, software means and data storage means used to analyse atomic coordinate data. The minimum hardware means of the computer-based systems of the present invention typically comprises a central processing unit (CPU), input means, output means and data storage means. Desirably a monitor is provided to visualise structure data. The data storage means may be RAM or means for accessing computer readable media of the invention. Examples of such systems are microcomputer workstations available from Silicon Graphics Incorporated and Sun Microsystems running Unix based, Windows NT or IBM OS/2 operating systems.

By "computer readable media" we mean any medium or media, which can be read and accessed directly by a computer e.g. so that the media is suitable for use in the above-mentioned computer system. Such media include, but are not limited to: magnetic storage media such as floppy discs, hard disc storage medium and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

The term "homologue" is used herein in two distinct senses. It is used *sensu stricto* to define proteins that share a common ancestor. In this sense it covers orthologues (species variants which have diverged in different organisms following a speciation event) and paralogues (variants which have diverged within the same organism after a gene duplication event). Thus, there is a direct evolutionary relationship between such homologues and this may be reflected in structural and/or functional similarities. For example, orthologues may perform the same role in each organism in which they are found, while paralogues may perform functionally related (but distinct) roles within the same organism.

The term is also used herein *sensu lato* to define proteins which are to some extent structurally similar (i.e. not necessarily evolutionary related and/or structurally and functionally equivalent). In this sense, homology is recognised on the basis of purely structural criteria by the presence of amino acid sequence identities and/or conservative amino acid changes and/or similar secondary, tertiary or quaternary structures.

The term "analogue" is used herein to define proteins with similar functions and/or structures and which are not necessarily evolutionary related. Protein analogues which

share function but which have no or little structural similarities are likely to have arisen by convergent evolution. Conversely, protein analogues which share structural similarities but which exhibit few or no functional similarities are likely to have arisen by divergent evolution. Protein analogues may be identified, for example, by screening a library of proteins to detect those with similar function(s) but different physical properties, or by screening for proteins which share structural features but not necessarily any functions (e.g. by immunological screening).

The term "equivalent" is used herein to define those protein analogues which exhibit substantially the same function(s) and which share at least some structural features (e.g. functional domains), but which have not evolved from a common ancestor. Such equivalents are typically synthetic proteins (see below) and may be generated, for example, by identifying sequences of functional importance (e.g. by identifying conserved or canonical sequences, functional domains or by mutagenesis followed by functional assay), selecting an amino acid sequence on that basis and then synthesising a peptide based on the selected amino acid sequence. Such synthesis can be achieved by any of many different methods known in the art, including solid phase peptide synthesis (to generate synthetic peptides) and the assembly (and subsequent cloning) of oligonucleotides. Some synthetic protein analogues may be chimaeras (see below), and such equivalents can be designed and assembled for example by concatenation of two or more different structural and/or functional peptide domains from different proteins using recombinant DNA techniques (see below).

The BACE protein homologues of the invention therefore include proteins and peptides having at least 75%, 80%, 85%, 90%, 95%, 97%, 98% or 99% sequence identity with the reference protein, and include truncated forms of the BACE proteins of the invention. Such truncates are preferably at least 25%, 35%, 50% or 75% of the length of the corresponding specifically exemplified proteins and may have at least 60% sequence identity (more preferably, at least 75%, 80%, 85%, 90% , 95%, 97%, 98% or 99% sequence identity) with that specifically exemplified protein.

Particularly preferred homologues are truncates that contain a segment preferably comprising at least 8, 15, 20 or 30 contiguous amino acids that share at least 75%, 80%, 85%, 90% , 95%, 97%, 98% or 99% sequence identity with that specifically exemplified protein.

A "conservative amino acid change" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g. lysine, arginine and histidine), acidic side chains (e.g. aspartic acid and glutamic acid), non-charged polar side chains (e.g. glycine, asparagine, glutamine, serine, threonine, tyrosine and cysteine), non-polar side chains (e.g. alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine and tryptophan), beta-branched side chains (e.g. threonine, valine and isoleucine), and aromatic side chains (e.g. tyrosine, phenylalanine, tryptophan and histidine).

Thus, references herein to proteins and peptides that are to some defined extent "identical" (or which share a defined extent of "identity") with a reference protein or peptide may also optionally be interpreted to include proteins and peptides in which conservative amino acid changes are disregarded so that the original amino acid and its changed counterpart are regarded as identical for the purposes of sequence comparisons.

The term "allelic form" is used herein to define a naturally-occurring alternative forms of the sequence present in the BACE protein which reflect naturally-occurring differences in the BACE gene pool. Preferably, allelic variants of the proteins of the invention have at least 60% sequence identity (more preferably, at least 75%, 80%, 85%, 90% or 95% sequence identity) with the corresponding specifically exemplified BACE protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The term "species variant" (or orthologue) is used herein to define the corresponding protein from a different organism. Thus, species variants share a direct evolutionary relationship.

The term "derivative" as applied herein to the BACE proteins of the invention is used to define proteins which are modified versions of the specifically exemplified proteins of the invention. Such derivatives may include fusion proteins, in which the proteins of the invention have been fused to one or more different proteins, peptides or amino acid tags (for example an antibody or a protein domain conferring a biochemical activity, to act as a label, or to facilitate purification). Particularly preferred are derivatives in which the peptides are

modified by a polyHis (6xHis) tag to facilitate purification of the peptide derivative on Ni^{2+} agarose beads.

The derivatives may also be products of synthetic processes that use a peptide of the invention as a starting material or reactant.

The term "mutein" is used herein to define proteins that are mutant forms of the BACE proteins of the invention, i.e. proteins in which one or more amino acids have been added, altered, deleted, replaced, inserted or substituted. Thus, the terms “BACE mutein” and “mutant BACE protein” are used interchangeably herein. The muteins/mutant BACE proteins of the invention therefore include fragments, truncates and fusion proteins and peptides (e.g. comprising fused immunoglobulin, receptor, tag, label or enzyme moieties).

The muteins of the invention therefore include truncated forms of the BACE proteins of the invention. Such truncates are preferably least 25%, 35%, 50% or 75% of the length of the corresponding specifically exemplified BACE protein and may have at least 60% sequence identity (more preferably, at least 75%, 80%, 85%, 90% or 95% sequence identity) with that specifically exemplified protein.

Particularly preferred are truncates that contain a segment preferably comprising at least 8, 15, 20 or 30 contiguous amino acids that share at least 75%, 80%, 85%, 90% or 95% sequence identity with that specifically exemplified protein.

For the purposes of the present invention, sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. In particular, sequence identity may be determined using any of a number of mathematical algorithms. A nonlimiting example of a mathematical algorithm used for comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87: 2264-2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90: 5873-5877.

Another example of a mathematical algorithm used for comparison of sequences is the algorithm of Myers and Miller (1988) CABIOS 4: 11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of

4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85: 2444-2448.

Preferred for use according to the present invention is the WU-BLAST (Washington University BLAST) version 2.0 software. WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from ftp ://blast. wustl. edu/blast/executables. This program is based on WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle ed., Methods in Enzymology 266: 460-480; Altschul et al., 1990, Basic local alignment search tool, Journal of Molecular Biology 215: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, Nature Genetics 3: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, Proc. Natl. Acad. Sci. USA 90: 5873-5877; all of which are incorporated by reference herein).

In all search programs in the suite the gapped alignment routines are integral to the database search itself. Gapping can be turned off if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

The muteins of the invention also include peptides in which mutations have been introduced which effectively promote or impair one or more activities of the protein, for example mutations which promote or impair the function of a receptor, a recognition sequence or an effector binding site.

Muteins may be produced by any convenient method. Conveniently, site-directed mutagenesis with mutagenic oligonucleotides may be employed using a double stranded template (pBluescript KS II construct containing nucleic acid encoding the BACE protein),

(e.g. Chameleon™ or QuikChange™ - Stratagene™) or cassette mutagenesis methods my be employed. After verifying each mutant derivative by sequencing, the mutated gene is excised and inserted into a suitable vector so that the modified protein can be over-expressed and purified.

Brief Description of the Drawings

Table 1, provides the coordinates of the BACE structure. The numbering of the residues used in this Table (see Section (D) below) correspond to the numbering of used by Hong *et al, ibid.* Elsewhere – unless indicated to the contrary – in the specification the numbering of the SwissProt database entry P56817 is used. Residue 1 of Table 1 corresponds to 62 of SwissProt P56817, and residue 385 corresponds to 446 of SwissProt P56817. In the sequence listing below, the SwissProt P56817 residues 14-453 are shown as 16-455 of SEQ ID NO:2.

Figure 1 represents the packing arrangements of the BACE monomers within the $P6_122$ crystal lattice.

Figure 2 shows the superposition of BACE in complex with OM99-2 (1FKN), in black, with BACE, of the invention, in the absence of ligand (grey). The position of OM99-2 is defined by a stick representation of the inhibitor.

Detailed Description of the Invention

A. Construct design

BACE protease is expressed, at high levels, as insoluble inclusion bodies in bacterial cells. To prepare functional protein appropriate for enzyme assay and structural studies these inclusion bodies are solubilised using denaturants and the slow removal of these denaturants results in the formation of the correct tertiary structure. In addition BACE is expressed as a pro-sequence and requires activation by a protease before it is fully functional.

One of the problems of the techniques described in the art (Tang *et al*) for isolation of BACE from inclusion bodies is the generation of a mixture of products from the uncontrolled cleavage process. Choppa *et al* describe the isolation of BACE from mammalian cells and the subsequent cleavage with protease, which also gives a mixture of

protein species. Thus there is a need in the art for a method of generating active BACE as a homogenous species.

A further problem with the prior art techniques is the low yield of crystallisable material obtained. The inventors surprisingly found that the present invention results in a high yield from bacterial cells, in particular *E. coli.*

The inventors utilized clostripain as an activating protease to perform this cleavage in a controlled manner but this produced multiple species of BACE, as determined by mass spectrometry. In order to obtain a uniform homogenous protein after activation, a number of different constructs were produced. These constructs focused on the mutation of two of the clostripain cleavage sites (R56 and R57).

The sequences of the invention were designed to achieve a single cleavage point upon activation by clostripain, as activation of wild type sequence in this way resulted in a non-crystallisable protein with heterogeneous N termini.

The BACE constructs of the invention contain successful modifications of the BACE sequence to allow generation of homogeneous protein product from the use of clostripain. The sequence of the invention contains substitution for another amino acid residue or deletion of the arginine 56 and/or arginine 57 (numbering based on wild type full length sequence, SWISS_PROT P56817). In a preferred aspect of the invention this is a conserved substitution. Conservative amino acid substitutions are well known in the art, and include substitutions made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the amino acid residues involved. For example, positively charged amino acids include lysine and arginine and histidine. In a preferred aspect the mutation introduced is substitution of arginine to lysine at position 56 and/or 57, more preferably 56 and 57. This results in, as oppose to the wild type, the production of a single species of activated protein upon limited digest with clostripain. Clostripain cleavage occurs at a single site and is thus specific and generates a single species in minutes.

The advantage of these mutations is that they allow the controlled cleavage at arginine residue 42 and hence provides a single N-terminus.

This controlled cleavage thus provides a means to produce a substantially homogeneous composition of a BACE protein of the invention. By substantially homogeneous, it is meant that at least 95%, preferably at least 98% and more preferably at least 99% of the BACE protein in the composition has the same N-terminus. The N-terminus may be selected from residues 43 (i.e. by cleavage at 42), 46, 56, 57 or 58, preferably from 43, 56, 57 or 58, more preferably 43, 56 or 57.

These mutations can be introduced onto any sequence of BACE by site-directed mutagenesis techniques, to facilitate the generation of homogeneous material for structural or activity studies. Thus proteins of the invention are BACE proteins with residues 56 and/or 57 either mutated or deleted. Proteins of the invention also include BACE mutants described below in section (C).

The invention is exemplified by several constructs (SEQ ID 5-18). These were built based on the wild type sequence (BACE WT, SEQ ID 2) where R56 and/or R57 were mutated to K or deleted. These were BACE WT R56KR57K (SEQ ID 6), BACE WT R57K (SEQ ID 8), BACE WT R57del (SEQ ID 10). This was also performed on the BACE construct BACE N->Q to give BACE N->Q R56KR57K (SEQ ID 12), BACE N->Q R57K (SEQ ID 16), BACE N->Q R57del (SEQ ID 18). The BACE N->Q construct contains 4 additional mutations of asparagines to glutamine and a C-terminal His tag as well as the arginine mutations. BACE N->Q without the His tag was mutated at 56 and 57 to give BACE N->Q R56K R57K no His (SEQ ID 14).

SEQ ID 19 is the activated from of SEQ ID 6, SEQ ID 21 the activated form of SEQ ID 12 and SEQ ID 20 the activated form of SEQ ID 14, i.e. the form in which the protein is crystallized.

The three BACE constructs BACE WT R56KR57K, BACE N->Q R56KR57K, and BACE N->Q R56KR57K no His gave higher expression levels.

Thus the invention concerns any BACE proteins with one or more of: a mutation at 56, and mutation at 57, or a deletion at 56 or a deletion at 57, but preferably 56 and 57 mutated, and crystals thereof i.e. any BACE protein comprising residues 56-396 of BACE (based on numbering of SwissProt P56817) and containing these mutations.

B. Refolding protocol

The protein was expressed in *E. coli* as inclusion bodies, as outlined above. In an improvement of existing techniques BACE isolated from inclusion bodies was refolded by the use of high pH, a sulfobetaine refolding agent, and a longer duration at high pH. This refolding protocol increased the yield of refolded protein obtained and also gave high and reproducible yields of refolded BACE suitable for crystallisation.

The use of high pH in refolding (Burton et el, 1989) and of sulfobetaines as solubilising molecules in folding experiments (Goldberg *et al*, 1996) has previously been described. Here we describe the use of a combination of these technologies to give an unprecedented high yield of BACE. In addition to this combination of high pH and sulfobetaine, in another deviation from existing protocols for refolding BACE, the pH is maintained at high pH for at least 2 weeks. This is in comparison to the method of Tang *et al*, where BACE is solubilised at high pH and then the pH lowered before protein recovery at least 2-3 weeks later, preferably 3-4 weeks later.

Another aspect of the invention therefore concerns a novel method of producing soluble BACE proteins of the invention, utilizing a refolding protocol comprising the combined techniques of high pH buffer and the use of sulfobetaine, and also maintaining this high pH over at least two weeks.

More specifically, a method for producing refolded recombinant BACE comprising refolding the BACE under conditions which denature and then slowly renature the enzyme into a soluble form wherein: (a) the BACE is solubilised using a chaotrope such as urea or guanidine at 8-10M (typically 8 M urea solution) including one or more reducing agents at a pH of greater than 8.0 e.g. pH 9.0-10.5; (b) the BACE is then diluted into an aqueous buffer, like 20 mM-Tris, pH 9.0, containing sulfobetaine, preferably 10 mM sulfobetaine, where the sulfobetaine is preferably NDSB256 (3-(benzyldimethylammonio) propanesulfonate); (c) the solution is maintained at low temperature, e.g. 3-6 °C typically 4 °C, and at high pH, typically approximately pH 9.0, for at least 2 weeks (typically 3 weeks, more typically 4 weeks) before proceeding with purification.

C. Protein Crystals.

Described herein is a crystal of BACE having a hexagonal space group $P6_122$, and unit cell dimensions a=b=103.2 Å, c=169.1 Å , $\alpha=\beta=60$ °, $\gamma=120$°. Unit cell variability of 5% may

be observed in all dimensions. Such crystals contain one copy of BACE in the asymmetric unit.

Such a crystal may be obtained using the methods described in the accompanying examples.

The crystal may be of the BACE protein of SEQ ID 19 although as explained earlier any homologue, allelic form, species variant, derivative or mutein (as hereinbefore defined) may be used. Thus, it will be understood by those of skill in the art that some variation to the primary amino acid sequence may be made without significant alteration to the resulting crystal structure. Such minor variations include the replacement of one or more amino acids, for example from 1 to 30, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids by an equivalent or fewer number of amino acids.

The methodology used to provide a BACE crystal illustrated herein may be used generally to provide a human BACE apo crystal resolvable at a resolution of at least 3 Å.

The invention thus further provides an apo BACE crystal having a resolution better than, i.e. numerically lower than, 2.5 Å.

The invention also provides a BACE crystal having a resolution better than, i.e. numerically lower than, 1.8 Å.

The invention also provides apo crystals of BACE resolvable to at least 2.5 Å capable of being soaked with compound(s) to form co-complex structures.

The proteins may be wild-type proteins or variants thereof, which are modified to promote crystal formation, for example by N-terminal truncations and/or deletion of loop regions, which prevent crystal formation.

The methods described herein may be used to make a BACE protein crystal, particularly of a BACE protein of SEQ ID 19-21, which method comprises growing a crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME, preferably 20-24 % PEG 5000 MME, more preferably 20-22.5 % PEG 5000 MME, with 180-220 mM (e.g. 200 mM) ammonium iodide and 180-220 mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6). In a preferred embodiment, this reservoir buffer may also contain from 0 to 5% glycerol, e.g. about 2.5% glycerol. The growing of the crystal is by vapour diffusion and is performed by placing an aliquot of the protein solution on a cover slip as a hanging drop

above a well containing the reservoir buffer. The concentration of the protein solution used was approximately 7 mg/ml.

Other crystals of the invention include crystals which have selected coordinates of the binding pocket, wherein the amino acid residues associated with those selected coordinates are located in a protein framework which holds these amino acids in a relative spatial configuration corresponding to the spatial configuration of those amino acids in Table 1. By "corresponding to", it is meant within an r.m.s.d. of less than 2.0 Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å and most preferably less than 0.5 Å from the Cα or backbone atoms of Table 1, preferably the Cα atoms.

Crystals of the invention also include crystals of BACE mutants (muteins). In addition, BACE mutants may be crystallized in co-complex with known BACE substrates or inhibitors or novel compounds.

As explained herein, a mutant BACE (or BACE mutein) is a BACE protein characterized by the replacement or deletion of at least one amino acid from the wild type BACE. Such a mutant may be prepared for example by site-specific mutagenesis, or incorporation of natural or unnatural amino acids.

As explained herein, the present invention therefore contemplates BACE mutants (or muteins) as hereinbefore defined.

For example, the BACE mutants may define a polypeptide which is obtained by replacing at least one amino acid residue in a native or synthetic BACE with a different amino acid residue and/or by adding and/or deleting amino acid residues within the native polypeptide or at the N- and/or C-terminus of a polypeptide corresponding to BACE, and which has substantially the same three-dimensional structure as BACE from which it is derived. By having substantially the same three-dimensional structure is meant having a set of atomic structure co-ordinates that have a root mean square deviation (r.m.s.d.) of less than or equal to about 2.0 Å (preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å and most preferably less than 0.5 Å) when superimposed with the atomic structure co-ordinates of the BACE from which the mutant is derived when at least about 50% to 100% of the C_α atoms of the BACE

are included in the superposition. A mutant may have, but need not have, enzymatic or catalytic activity.

To produce homologues or mutants, amino acids present in the said protein can be replaced by other amino acids having similar properties, for example hydrophobicity, hydrophobic moment, antigenicity, propensity to form or break α-helical or β-sheet structures, and so. Substitutional variants of a protein are those in which at least one amino acid in the protein sequence has been removed and a different residue inserted in its place. Amino acid substitutions are typically of single residues but may be clustered depending on functional constraints e.g. at a crystal contact. Preferably amino acid substitutions will comprise conservative amino acid substitutions. Insertional amino acid variants are those in which one or more amino acids are introduced. This can be amino-terminal and/or carboxy-terminal fusion as well as intrasequence. Examples of amino-terminal and/or carboxy-terminal fusions are affinity tags, MBP tag, and epitope tags.

Deletional variants are those in which one or more amino acids are removed. This can be amino-terminal and/or carboxy-terminal, or in an internal region (for example a loop region), for example to remove or shorten that region.

Amino acid substitutions, deletions and additions that do not significantly interfere with the three-dimensional structure of the BACE will depend, in part, on the region of the BACE where the substitution, addition or deletion occurs. In highly variable regions of the molecule, non-conservative substitutions as well as conservative substitutions may be tolerated without significantly disrupting the three-dimensional structure of the molecule. In highly conserved regions, or regions containing significant secondary structure, conservative amino acid substitutions are preferred.

As explained earlier, conservative amino acid substitutions are well known in the art, and include substitutions made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the amino acid residues involved. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; amino acids with uncharged polar head groups having similar hydrophilicity values include the following: leucine, isoleucine, valine; glycine, alanine; asparagine, glutamine; serine, threonine;

phenylalanine, tyrosine. Other conservative amino acid substitutions are well known in the art.

In some instances, it may be particularly advantageous or convenient to substitute, delete and/or add amino acid residues to a BACE binding pocket or catalytic residue in order to provide convenient cloning sites in the cDNA encoding the polypeptide, to aid in purification of the polypeptide, to modify compound binding etc. Such substitutions, deletions and/or additions which do not substantially alter the three dimensional structure of BACE will be apparent to those having skills in the art.

It should be noted that the mutants (BACE muteins) contemplated herein need not exhibit enzymatic activity. Indeed, amino acid substitutions, additions or deletions that interfere with the catalytic activity of the BACE but which do not significantly alter the three-dimensional structure of the catalytic region are specifically contemplated by the invention. Such crystalline polypeptides, or the atomic structure co-ordinates obtained there from, can be used to identify compounds that bind to the protein.

The crystallization of such mutants and the determination of the three-dimensional structures by X-ray crystallography relies on the ability of the mutant proteins to yield crystals that diffract at high resolution. The mutant protein could then be used to obtain information on compound binding through the determination of mutant protein/ligand complex structures, which may be characterized using the BACE crystal structure of Table 1.

The mutations can be introduced by site-directed mutagenesis e.g. using a Stratagene QuikChange™ Site-Directed Mutagenesis Kit or cassette mutagenesis methods (see e.g. Ausubel et al., eds., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., New York, and Sambrook et al., *Molecular Cloning: a Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)).

To the extent that the present invention relates to BACE-ligand complexes and mutant, homologue, allelic form, species variant, derivative, mutein and analogue proteins of BACE, crystals of such proteins may be formed. The skilled person would recognize that the conditions provided herein for crystallising BACE may be used to form such crystals. Alternatively, the skilled person would use the conditions as a basis for identifying modified conditions for forming the crystals.

Thus the aspects of the invention relating to crystals of BACE, may be extended to crystals of mutant/mutein, homologue, allelic form, species variant or derivative (as defined herein).

D. Crystal Coordinates

In a further aspect, the invention also provides an apo crystal structure of BACE having the three dimensional atomic coordinates of Table 1. An advantageous feature of the structure defined by the atomic coordinates is that it has a high resolution of about 1.75 Å. A further advantageous aspect is the provision of an apo structure of BACE, which contains no ligand bound, unlike those previously described in the art. This is particularly advantageous as ligands can then be easily soaked into the crystal to provide co-complex data without the need for removal of any ligand already present, and without the need for time-consuming co-crystallisation experiments.

The BACE structure set out in Table 1 is a monomer structure. This is the first time that a monomer has been observed crystallographically for this protein.

Table 1 gives atomic coordinate data for BACE. In Table 1 the third column denotes the atom type, the fourth the residue type, the fifth the chain identification, the sixth the residue number (the atom numbering as described in Hong *et al*, 2000) the seventh, eighth and ninth columns are the X, Y, Z coordinates respectively of the atom in question, the tenth column the occupancy of the atom, the eleventh the temperature factor of the atom, the twelfth the chain identification, and the last, thirteenth column, the atom type.

Each of the tables is presented in an internally consistent format. For example, in Table 1 the coordinates of the atoms of each amino acid residue are listed such that the backbone nitrogen atom is first, followed by the C-alpha backbone carbon atom, designated CA, followed by the carbon and oxygen of the protein backbone and finally side chain residues (designated according to one standard convention). Alternative file formats (e.g. such as a format consistent with that of the EBI Macromolecular Structure Database (Hinxton, UK)) which may include a different ordering of these atoms, or a different designation of the side-chain residues, may be used or preferred by others of skill in the art. However it will be apparent that the use of a different file format to present or manipulate the coordinates of the Tables is within the scope of the present invention.

The coordinates of Table 1 provide a measure of atomic location in Ångstroms, to 3 decimal places. The coordinates are a relative set of positions that define a shape in three dimensions, but the skilled person would understand that an entirely different set of coordinates having a different origin and/or axes could define a similar or identical shape. Furthermore, the skilled person would understand that varying the relative atomic positions of the atoms of the structure so that the root mean square deviation of the residue backbone atoms (i.e. the nitrogen-carbon-carbon backbone atoms of the protein amino acid residues) is less than 2.0 Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å and most preferably less than 0.5 Å when superimposed on the coordinates provided in Table 1 for the Cα atoms or residue backbone atoms, will generally result in a structure which is substantially the same as the structure of Table 1 in terms of both its structural characteristics and usefulness for structure-based analysis of BACE-interactivity molecular structures.

Likewise the skilled person would understand that changing the number and/or positions of the water molecules and/or substrate molecules of Table 1 will not generally affect the usefulness of the structure for structure-based analysis of BACE-interacting structure. Thus for the purposes described herein as being aspects of the present invention, it is within the scope of the invention if: the Table 1 coordinates are transposed to a different origin and/or axes; the relative atomic positions of the atoms of the structure are varied so that the root mean square deviation of residue backbone atoms is less than 2.0 Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å, and most preferably less than 0.5 Å when superimposed on the coordinates provided in Table 1 for the Cα or residue backbone atoms; and/or the number and/or positions of water molecules and/or substrate molecules is varied.

Reference herein to the coordinate data of Table 1 and the like thus includes the coordinate data in which one or more individual values of the Table are varied in this way unless specified explicitly to the contrary. In a preferred aspect, reference herein to the coordinates of Table 1 or parts thereof (e.g. selected coordinates) should be taken to include coordinates having a root mean square deviation of less than 0.72 Å, and preferably less than 0.5 Å, from the Cα atoms of Table 1 or corresponding parts thereof.

By "root mean square deviation" we mean the square root of the arithmetic mean of the squares of the deviations from the mean.

Protein structure similarity is routinely expressed and measured by the root mean square deviation (r.m.s.d.), which measures the difference in positioning in space between two sets of atoms. The r.m.s.d. measures distance between equivalent atoms after their optimal superposition. The r.m.s.d. can be calculated over all atoms, over residue backbone atoms (i.e. the nitrogen-carbon-carbon backbone atoms of the protein amino acid residues), main chain atoms only (i.e. the nitrogen-carbon-oxygen-carbon backbone atoms of the protein amino acid residues), side chain atoms only or more usually over C-alpha atoms only. For the purposes of this invention, the r.m.s.d. can be calculated over any of these, using any of the methods outlined below.

Methods of comparing protein structures are discussed in Methods of Enzymology, vol 115, pg 397-420. The necessary least-squares algebra to calculate r.m.s.d. has been given by Rossman and Argos (J. Biol. Chem. , vol 250, pp7525 (1975)) although faster methods have been described by Kabsch (Acta Crystallogr., Section A, A92, 922 (1976); Acta Cryst. A34, 827-828 (1978)), Hendrickson (Acta Crystallogr., Section A, A35, 158 (1979) and McLachan (J. Mol. Biol., vol 128, pp49 (1979). Some algorithms use an iterative procedure in which the one molecule is moved relative to the other, such as that described by Ferro and Hermans (Ferro and Hermans, Acta Crystallographic, A33, 345-347 (1977)). Other methods e.g. Kabsch's algorithm locate the best fit directly.

It is usual to consider C-alpha atoms and the rmsd can then be calculated using programs such as LSQKAB (Collaborative Computational Project 4. The CCP4 Suite: Programs for Protein Crystallography, *Acta Crystallographica*, D50, (1994), 760-763), MNYFIT (part of a collection of programs called COMPOSER, Sutcliffe, M.J., Haneef, I., Carney, D. and Blundell, T.L. (1987) Protein Engineering, 1, 377-384), MAPS (Lu, G. An Approach for Multiple Alignment of Protein Structures (1998, in manuscript)), QUANTA (Jones et al., Acta Crystallography A47 (1991), 110-119 and commercially available from Accelerys, San Diego, CA), Insight (commercially available from Accelerys, San Diego, CA), Sybyl® (commercially available from Tripos, Inc., St Louis), O (Jones et al., *Acta Crystallographica*, A47, (1991), 110-119), and other coordinate fitting programs.

In, for example the programs LSQKAB and O, the user can define the residues in the two proteins that are to be paired for the purpose of the calculation. Alternatively, the pairing of residues can be determined by generating a sequence alignment of the two proteins, programs for sequence alignment are discussed in more detail in Section G. The atomic

coordinates can then be superimposed according to this alignment and an r.m.s.d. value calculated. The program Sequoia (C.M. Bruns, I. Hubatsch, M. Ridderström, B. Mannervik, and J.A. Tainer (1999) Human Glutathione Transferase A4-4 Crystal Structures and Mutagenesis Reveal the Basis of High Catalytic Efficiency with Toxic Lipid Peroxidation Products, *Journal of Molecular Biology* 288(3): 427-439) performs the alignment of homologous protein sequences, and the superposition of homologous protein atomic coordinates. Once aligned, the r.m.s.d. can be calculated using programs detailed above. For sequence identical, or highly identical, the structural alignment of proteins can be done manually or automatically as outlined above. Another approach would be to generate a superposition of protein atomic coordinates without considering the sequence.

It is more normal when comparing significantly different sets of coordinates to calculate the r.m.s.d. value over C-alpha atoms only. It is particularly useful when analysing side chain movement to calculate the r.m.s.d. over all atoms and this can be done using LSQKAB and other programs.

Varying the atomic positions of the atoms of the structure by up to about 0.5 Å in a concerted way, preferably up to about 0.3 Å in any direction will result in a structure which is substantially the same as the structure of Table 1 in terms of both its structural characteristics and utility e.g. for molecular structure-based analysis.

Also, modifications in the BACE crystal structure due to e.g. mutations, additions, substitutions, and/or deletions of amino acid residues (including the deletion of one or more BACE protomers) could account for variations in the BACE atomic coordinates. However, atomic coordinate data of BACE modified so that a ligand that bound to one or more binding sites of BACE would be expected to bind to the corresponding binding sites of the modified BACE are, for the purposes described herein as being aspects of the present invention, also within the scope of the invention. Reference herein to the coordinates of Table 1 thus includes the coordinates modified in this way. Preferably, the modified coordinate data define at least one BACE binding cavity.

Those of skill in the art will appreciate that in many applications of the invention, it is not necessary to utilise all the coordinates of Table 1, but merely a portion of them. The term portion is intended to define a sub-set of the coordinates, which may or may not represent contiguous amino acid residues in the BACE structure. For example, as described below, in

methods of modelling candidate compounds with BACE, selected coordinates of BACE may be used, for example at least 5, preferably at least 10, more preferably at least 50 and even more preferably at least 100 atoms of the BACE structure. Likewise, the other applications of the invention described herein, including homology modelling and structure solution, and data storage and computer assisted manipulation of the coordinates, may also utilise all or a portion of the coordinates of Table 1.

E. Homology Modelling

The invention also provides a means for homology modelling of other proteins (referred to below as target BACE proteins). By "homology modelling", it is meant the prediction of related BACE structures based either on X-ray crystallographic data or computer-assisted *de novo* prediction of structure, based upon manipulation of the coordinate data of Table 1.

"Homology modelling" extends to target BACE proteins, which are analogues or homologues of the BACE protein whose structure has been determined in the accompanying examples. It also extends to BACE protein mutants of BACE protein itself.

The term "homologous regions" describes amino acid residues in two sequences that are identical or have similar (e.g. aliphatic, aromatic, polar, negatively charged, or positively charged) side-chain chemical groups. Identical and similar residues in homologous regions are sometimes described as being respectively "invariant" and "conserved" by those skilled in the art.

In general, the method involves comparing the amino acid sequences of the BACE protein of Table 1 with a target BACE protein by aligning the amino acid sequences (Dunbrack et al., *Folding and Design*, 2, (1997), 27-42). Amino acids in the sequences are then compared and groups of amino acids that are homologous (conveniently referred to as "corresponding regions") are grouped together. This method detects conserved regions of the polypeptides and accounts for amino acid insertions or deletions.

Homology between amino acid sequences can be determined using commercially available algorithms. The programs *BLAST*, *gapped BLAST*, *BLASTN*, *PSI-BLAST* and *BLAST 2* sequences (provided by the National Center for Biotechnology Information) are widely used in the art for this purpose, and can align homologous regions of two amino acid sequences. These may be used with default parameters to determine the degree of homology between

the amino acid sequence of the Table 1 protein and other target BACE proteins, which are to be modeled.

Analogues are defined as proteins with similar three-dimensional structures and/or functions with little evidence of a common ancestor at a sequence level.

Homologues are defined as proteins with evidence of a common ancestor, i.e. likely to be the result of evolutionary divergence and are divided into remote, medium and close sub-divisions based on the degree (usually expressed as a percentage) of sequence identity.

A homologue is defined here as a protein with at least 15% sequence identity or which has at least one functional domain, which is characteristic of BACE.

There are two types of homologue: orthologues and paralogues. Orthologues are defined as homologous genes in different organisms, i.e. the genes share a common ancestor coincident with the speciation event that generated them. Paralogues are defined as homologous genes in the same organism derived from a gene/chromosome/ genome duplication, i.e. the common ancestor of the genes occurred since the last speciation event.

The homologues could also be mutants as described in section (C).

Once the amino acid sequences of the polypeptides with known and unknown structures are aligned, the structures of the conserved amino acids in a computer representation of the polypeptide with known structure are transferred to the corresponding amino acids of the polypeptide whose structure is unknown. For example, a tyrosine in the amino acid sequence of known structure may be replaced by a phenylalanine, the corresponding homologous amino acid in the amino acid sequence of unknown structure.

The structures of amino acids located in non-conserved regions may be assigned manually by using standard peptide geometries or by molecular simulation techniques, such as molecular dynamics. The final step in the process is accomplished by refining the entire structure using molecular dynamics and/or energy minimization.

Homology modelling as such is a technique that is well known to those skilled in the art (see e.g. Greer, *Science*, Vol. 228, (1985), 1055, and Blundell *et al.*, *Eur. J. Biochem*, Vol. 172, (1988), 513). The techniques described in these references, as well as other homology

modelling techniques, generally available in the art, may be used in performing the present invention.

Thus the invention provides a method of homology modelling comprising the steps of: (a) aligning a representation of an amino acid sequence of a target BACE protein of unknown three-dimensional structure with the amino acid sequence of the BACE of Table 1 to match homologous regions of the amino acid sequences; (b) modelling the structure of the matched homologous regions of said target BACE of unknown structure on the corresponding regions of the BACE structure as defined by Table 1; and (c) determining a conformation (e.g. so that favorable interactions are formed within the target BACE of unknown structure and/or so that a low energy conformation is formed) for said target BACE of unknown structure which substantially preserves the structure of said matched homologous regions.

Preferably one or all of steps (a) to (c) are performed by computer modelling.

The aspects of the invention described herein which utilise the BACE structure *in silico* may be equally applied to homologue models of BACE obtained by the above aspect of the invention, and this application forms a further aspect of the present invention. Thus having determined a conformation of a BACE by the method described above, such a conformation may be used in a computer-based method of rational drug design as described herein.

The absence of a ligand from our structure is particularly advantageous for modelling of other proteins as this structure reveals the native structure of the protein unaffected by conformational changes upon ligand binding.

F. Structure Solution

The structure of the human BACE can also be used to solve the crystal structure of other target BACE proteins including other crystal forms of BACE, mutants, and co-complexes of BACE, where X-ray diffraction data or NMR spectroscopic data of these target BACE proteins has been generated and requires interpretation in order to provide a structure.

In the case of BACE, this protein may crystallize in more than one crystal form. The structure coordinates of BACE, or portions thereof, as provided by this invention are particularly useful to solve the structure of those other crystal forms of BACE. They may also be used to solve the structure of BACE mutants, BACE co-complexes, or of the

crystalline form of any other protein with significant amino acid sequence homology to any functional domain of BACE.

In the case of other target BACE proteins, particularly the BACE proteins referred to in Section C above, the present invention allows the structures of such targets to be obtained more readily where raw X-ray diffraction data is generated.

Thus, where X-ray crystallographic or NMR spectroscopic data is provided for target BACE-ligand complex, or a BACE homologue or analogue of unknown three-dimensional structure, the structure of BACE, as defined by Table 1, may be used to interpret that data to provide a likely structure for the other BACE by techniques which are well known in the art, e.g. phasing in the case of X-ray crystallography and assisting peak assignments in NMR spectra.

One method that may be employed for these purposes is molecular replacement. In this method, the unknown crystal structure, whether it is another crystal form of BACE, a BACE mutant, or a BACE co-complex, or the crystal of a target BACE protein with amino acid sequence homology to any functional domain of BACE, may be determined using the BACE structure coordinates of this invention as provided herein. This method will provide an accurate structural form for the unknown crystal more quickly and efficiently than attempting to determine such information *ab initio*.

Examples of computer programs known in the art for performing molecular replacement are CNX (Brunger A.T.; Adams P.D.; Rice L.M., Current Opinion in Structural Biology, Volume 8, Issue 5, October 1998, Pages 606-611 (also commercially available from Accelerys San Diego, CA) or AMORE (Navaza, J. (1994). AMoRe: an automated package for molecular replacement. Acta Cryst. A50, 157-163).

Thus, in a further aspect of the invention provides a method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1, and either (a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or (b) assigning NMR spectra Peaks of said protein by manipulating the coordinates of Table 1.

In a preferred aspect of this invention the co-ordinates are used to solve the structure of target BACE particularly homologues of BACE for example aspartic proteases such as BACE2 or cathepsin E (69% and 37% similarity, respectively).

G. Computer Systems

In another aspect, the present invention provides systems, particularly a computer system, the systems containing either (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a target BACE protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

For example the computer system may comprise: (i) a computer-readable data storage medium comprising data storage material encoded with the computer-readable data; (ii) a working memory for storing instructions for processing said computer-readable data; and (iii) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-readable data and thereby generating structures and/or performing rational drug design. The computer system may further comprise a display coupled to said central-processing unit for displaying said structures.

The invention also provides such systems containing atomic coordinate data of target BACE proteins wherein such data has been generated according to the methods of the invention described herein based on the starting data provided by Table 1.

Such data is useful for a number of purposes, including the generation of structures to analyze the mechanisms of action of BACE proteins and/or to perform rational drug design of compounds which interact with BACE, such as compounds which are inhibitors of BACE.

In another aspect, the invention provides a computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion (e.g. selected coordinates as defined herein) of the structure coordinates of BACE of Table 1, or a homologue of BACE, wherein said homologue comprises backbone atoms that have a root mean square deviation from the Cα or backbone atoms (nitrogen-carbon$_{\alpha}$-carbon) of Table 1 of less than 2 Å, such as not more than 1.5Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.74 Å, even more preferably less than 0.72 Å and most preferably less than 0.5 Å.

The invention also provides a computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for BACE according to Table 1; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

In a further aspect, the present invention provides computer readable media with with at least one of: (a) atomic coordinate data according to Table 1 recorded thereon, said data defining the three-dimensional structure of BACE, or at least selected coordinates thereof; (b) structure factor data for BACE recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a BACE-ligand complex or a BACE homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

By providing such computer readable media, the atomic coordinate data can be routinely accessed to model BACE or selected coordinates thereof. For example, RASMOL (Sayle et al., *TIBS*, Vol. 20, (1995), 374) is a publicly available computer software package which allows access and analysis of atomic coordinate data for structure determination and/or rational drug design.

On the other hand, structure factor data, which are derivable from atomic coordinate data (see e.g. Blundell et al., in *Protein Crystallography*, Academic Press, New York, London and San Francisco, (1976)), are particularly useful for calculating e.g. difference Fourier electron density maps.

A further aspect of the invention provides a method of providing data for generating structures and/or performing rational drug design for BACE, BACE homologues or analogues, complexes of BACE with a potential modulator, or complexes of BACE homologues or analogues with potential modulators, the method comprising:

(i) establishing communication with a remote device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE, at least one sub-domain of the three-dimensional structure of BACE, or the coordinates of a plurality of atoms of BACE; (b) structure factor data for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE homologue or analogue generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and (ii) receiving said computer-readable data from said remote device.

Thus the remote device may comprise e.g. a computer system or computer readable media of one of the previous aspects of the invention. The device may be in a different country or jurisdiction from where the computer-readable data is received. The communication may be via the internet, intranet, e-mail etc. Typically the communication will be electronic in nature, but some or all of the communication pathway may be optical, for example, over optical fibres. Additionally, the communication may be through radio signals or satellite transmissions.

H. Uses of the Crystals of the Invention

The crystal structures obtained according to the present invention (including the structure of Table 1 as well the structures of target BACE proteins obtained in accordance with the methods described herein), may be used in several ways for drug design.

By identifying conditions under which high quality crystals of apo-BACE can be produced (i.e. crystals which can diffract X-rays for the determination of atomic coordinates to a resolution of better than 2.5 Å), the present invention facilitates the identification of modulators of BACE activity.

The invention is particularly suitable for the design, screening, development and optimization of BACE inhibitor components. It is thus a preferred aspect of the invention that modulators are inhibitors.

In a further aspect, the invention provides a method for determining the structure of a compound bound to BACE, said method comprising: (a) providing a crystal of BACE according to the invention; (b) soaking the crystal with said compounds; and (c) determining the structure of said BACE compound complex by employing the data of Table 1.

Alternatively, the BACE and compound may be co-crystallized. Thus the invention provides a method for determining the structure of a compound bound to BACE, said method comprising; mixing the protein with the compound(s), crystallizing the protein-compound(s) complex; and determining the structure of said BACE-compound(s) complex by reference to the data of Table 1.

A mixture of compounds may be soaked or co-crystallized with the crystal, wherein only one or some of the compounds may be expected to bind to the BACE. As well as the structure of the complex, the identity of the complexing compound(s) is/are then determined.

In either case, substrate or a substrate analogue thereof may optionally be present.

The method may comprise the further steps of: (a) obtaining or synthesising said candidate modulator; (b) forming a complex of BACE and said candidate modulator; and (c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said candidate modulator to interact with BACE.

The analysis of such structures may employ (i) X-ray crystallographic diffraction data from the complex and (ii) a three-dimensional structure of BACE, or at least selected coordinates thereof, to generate a difference Fourier electron density map of the complex, the three-

dimensional structure being defined by atomic coordinate data according to Table 1. The difference Fourier electron density map may then be analyzed, to identify the binding mode of the modulator.

Therefore, such complexes can be crystallized and analyzed using X-ray diffraction methods, e.g. according to the approach described by Greer et al., *J. of Medicinal Chemistry*, Vol. 37, (1994), 1035-1054, and difference Fourier electron density maps can be calculated based on X-ray diffraction patterns of soaked crystals of BACE or co-crystallized BACE and the solved structure of uncomplexed BACE. These maps can then be analyzed e.g. to determine whether and where a particular compound binds to BACE and/or changes the conformation of BACE.

Electron density maps can be calculated using programs such as those from the CCP4 computing package (Collaborative Computational Project 4. The CCP4 Suite: Programs for Protein Crystallography, *Acta Crystallographica*, D50, (1994), 760-763.). For map visualization and model building programs such as "O" (Jones et al., *Acta Crystallographica*, A47, (1991), 110-119) or "QUANTA" (1994, San Diego, CA: Molecular Simulations can be used.

The crystal structures of a series of complexes may then be solved by molecular replacement and compared with that of the BACE of Table 1. Potential sites for modification within the various binding sites of the enzyme may thus be identified. This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between BACE and a chemical entity or compound.

All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined against 1.5 to 3.5 Å resolution X-ray data to an R value of about 0.30 or less using computer software, such as CNX (Brunger et al., *Current Opinion in Structural Biology*, Vol. 8, Issue 5, October 1998, 606-611, and commercially available from Accelerys, San Diego, CA), X-PLOR (Yale University, ©1992, distributed by Accelerys), as described by Blundell et al, (1976) and Methods in Enzymology, vol. 114 & 115, H. W. Wyckoff et al., eds., Academic Press (1985).

This information may thus be used to optimize known classes of BACE substrates or inhibitors, and more importantly, to design and synthesize novel classes of BACE inhibitors.

Analysing the complex by X-ray crystallography will determine the ability of the candidate compound to interact with BACE. Analysis of the co-complexes of BACE may involve e.g. phasing, molecular replacement or calculating a Fourier difference map of the complex as discussed above. However, with the high resolutions obtainable with the crystal, it can also be possible to determine the ability of the candidate modulator to interact with BACE merely by comparing the intensities and/or positions of X-ray diffraction spots from the complex with e.g. diffraction spots of uncomplexed BACE or a previously identified BACE-ligand complex. Thus the step of analysing the complex may involve analysing the intensities and/or positions of X-ray diffraction spots from the complex to determine the ability of the candidate modulator to interact with BACE.

Having obtained and characterized a modulator compound according to the invention, the invention further provides a method for modulating the activity of BACE which method comprises: (a) providing BACE under conditions where, in the absence of modulator, the BACE is able to synthesize amyloid β-peptide from amyloid precursor protein (APP); (b) providing a modulator compound; and (c) determining the extent to which the activity of BACE is altered by the presence of said compound.

I. Structure-based Drug Design

Determination of the three-dimensional structure of BACE provides important information about the binding sites of BACE, particularly when comparisons are made with similar enzymes. This information may then be used for rational design of BACE inhibitors, e.g. by computational techniques which identify possible binding ligands for the binding sites, by enabling linked-fragment approaches to drug design, and by enabling the identification and location of bound ligands using X-ray crystallographic analysis. These techniques are discussed in more detail below.

Greer *et al.* (1994) describes an iterative approach to ligand design based on repeated sequences of computer modelling, protein-ligand complex formation and X-ray crystallographic or NMR spectroscopic analysis. Thus novel thymidylate synthase inhibitor series were designed *de novo* by Greer *et al.*, and BACE inhibitors may also be designed in

the this way. More specifically, using e.g. GRID on the solved 3D structure of BACE, a ligand (e.g. a potential inhibitor) for BACE may be designed that complements the functionalities of the BACE binding sites. The ligand can then be synthesised, formed into a complex with BACE, and the complex then analysed by X-ray crystallography to identify the actual position of the bound ligand. The structure and/or functional groups of the ligand can then be adjusted, if necessary, in view of the results of the X-ray analysis, and the synthesis and analysis sequence repeated until an optimised ligand is obtained. Related approaches to structure-based drug design are also discussed in Bohacek *et al.*, Medicinal Research Reviews, Vol.16, (1996), 3-50.

Linked-fragment approaches to drug design also require accurate information on the atomic coordinates of target receptors. The basic idea behind these approaches is to determine (computationally or experimentally) the binding locations of plural ligands to a target molecule, and then construct a molecular scaffold to connect the ligands together in such a way that their relative binding positions are preserved. The ligands may be provided computationally and modelled in a computer system, or provided in an experimental setting, wherein crystals according to the invention are provided and a plurality of ligands soaked separately or in mixed pools into the crystal prior to X-ray analysis and determination of their location.

The binding site of two or more ligands are determined and may be connected to form a potential lead compound that can be further refined using e.g. the iterative technique of *Greer* et al. For a virtual linked-fragment approach see Verlinde et al., *J. of Computer-Aided Molecular Design*, 6, (1992), 131-147, and for NMR and X-ray approaches see Shuker et al., *Science*, 274, (1996), 1531-1534 and Stout et al., *Structure*, 6, (1998), 839-848. The use of these approaches to design BACE inhibitors is made possible by the determination of the BACE structure.

Many of the techniques and approaches to structure-based drug design described above rely at some stage on X-ray analysis to identify the binding position of a ligand in a ligand-protein complex. A common way of doing this is to perform X-ray crystallography on the complex, produce a difference Fourier electron density map, and associate a particular pattern of electron density with the ligand. However, in order to produce the map (as explained e.g. by Blundell *et al.* (1976)) it is necessary to know beforehand the protein 3D structure (or at least the protein structure factors). Therefore, determination of the BACE

structure also allows difference Fourier electron density maps of BACE-ligand complexes to be produced, which can greatly assist the process of rational drug design.

The provision of the crystal structures of the invention will also allow the development of compounds which interact with the binding pocket regions of BACE (for example to act as inhibitors of a BACE) based on a fragment linking or fragment growing approach.

For example, the binding of one or more molecular fragments can be determined in the protein binding pocket by X-ray crystallography. Molecular fragments are typically compounds with a molecular weight between 100 and 200 Da (Carr et al, 2002). This can then provide a starting point for medicinal chemistry to optimize the interactions using a structure-based approach. The fragments can be combined onto a template or used as the starting point for 'growing out' an inhibitor into other pockets of the protein (Blundell et al, 2002). The fragments can be positioned in the binding pocket of BACE and then 'grown' to fill the space available, exploring the electrostatic, van der Waals or hydrogen-bonding interactions that are involved in molecular recognition. The potency of the original weakly binding fragment thus can be rapidly improved using iterative structure-based chemical synthesis.

At one or more stages in the fragment growing approach, the compound may be synthesized and tested in a biological system for its activity. This can be used to guide the further growing out of the fragment.

Where two fragment-binding regions are identified, a linked fragment approach may be based upon attempting to link the two fragments directly, or growing one or both fragments in the manner described above in order to obtain a larger, linked structure, which may have the desired properties.

The previous aspects of the invention relate also to fragment linking or fragment growing approaches to rational drug design. Thus the step of providing the structure of a candidate modulator molecule in the previous aspects may be performed by providing the structures of a plurality of molecular fragments and linking the molecular fragments to form a candidate modulator molecule. Furthermore the step of fitting the structure of the candidate modulator molecule in the previous aspects may be performed by fitting the structure of each of the molecular fragments (before or after the molecular fragments are linked together).

For example, the computer-based method of rational drug design may comprise:

(a) providing the coordinates of at least two atoms of the BACE of Table 1; (b) providing the structures of a plurality of molecular fragments; (c) fitting the structure of each of the molecular fragments to the selected coordinates of the BACE; and (d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

In practice, it will be desirable to model a sufficient number of atoms of the BACE as defined by the coordinates of Table 1, which represent a binding pocket. Thus, in this embodiment of the invention, there will preferably be provided the coordinates of at least 5, preferably at least 10, more preferably at least 50 and even more preferably at least 100 preferably at least 500 selected atoms of the BACE structure.

A further aspect of the invention provides a compound having a chemical structure selected using the method of any one of the previous aspects, said compound being an inhibitor of BACE.

J. Uses of the Coordinates of the Invention in *in silico* analysis and design

Although the invention will facilitate the determination of actual crystal structures comprising BACE and a compound, which modulates BACE, current computational techniques provide a powerful alternative to the need to generate such crystals and generate and analyze diffraction data. Accordingly, a particularly preferred aspect of the invention relates to *in silico* methods directed to the analysis and development of compounds, which interact, with BACE structures of the present invention.

The approaches to structure-based drug design described below all require initial identification of possible compounds for interaction with target bio-molecule (in this case BACE). Sometimes these compounds are known e.g. from the research literature. However, when they are not, or when novel compounds are wanted, a first stage of the drug design program may involve computer-based *in silico* screening of compound databases (such as the Cambridge Structural Database) with the aim of identifying compounds which interact with the binding site or sites of the target bio-molecule. Screening selection criteria may be based on pharmacokinetic properties such as metabolic stability and toxicity. However, determination of the BACE structure allows the architecture and chemical nature of each BACE binding site to be identified, which in turn allows the geometric and

functional constraints of a descriptor for the potential inhibitor to be derived. The descriptor is, therefore, a type of virtual 3-D pharmacophore, which can also be used as selection criteria or filter for database screening.

Thus as a result of the determination of the BACE three-dimensional structure, more purely computational techniques for rational drug design may also be used to design BACE inhibitors (for an overview of these techniques see e.g. Walters et al (*Drug Discovery Today*, Vol.3, No.4, (1998), 160-178; Abagyan, R.; Totrov, M. *Curr. Opin. Chem. Biol.* **2001,** *5*, 375-382). For example, automated ligand-receptor docking programs (discussed e.g. by Jones et al. in *Current Opinion in Biotechnology*, Vol.6, (1995), 652-656 and Halperin, I.; Ma, B.; Wolfson, H.; Nussinov, R. *Proteins* **2002,** *47*, 409-443), which require accurate information on the atomic coordinates of target receptors may be used to design potential BACE inhibitors.

The aspects of the invention described herein which utilize the BACE structure *in silico* may be equally applied to both the BACE structure of Table 1 and the models of target BACE proteins obtained by other aspects of the invention. Thus having determined a conformation of a BACE by the method described above, such a conformation may be used in a computer-based method of rational drug design as described herein. In addition the availability of the structure of the BACE will allow the generation of highly predictive pharmacophore models for virtual library screening or compound design.

Accordingly, the invention provides a computer-based method for the analysis of the interaction of a molecular structure with a BACE structure of the invention, which comprises: (a) providing the structure of a BACE of the invention of Table 1; (b) providing a molecular structure to be fitted to said BACE structure; and (c) fitting the molecular structure to the BACE structure of Table 1.

In an alternative aspect, the method of the invention may utilize the coordinates of atoms of interest of BACE, which are in the vicinity of a putative molecular structure binding region, for example within 10-25 Å of the catalytic regions or within 5-10 Å of a compound bound, in order to model the pocket in which the structure binds. These coordinates may be used to define a space, which is then analyzed "*in silico*". Thus the invention provides a computer-based method for the analysis of molecular structures which comprises: (a) providing the coordinates of at least two atoms of a BACE structure of the invention ("selected

coordinates"); (b) providing the structure of a molecular structure to be fitted to said coordinates; and (c) fitting the structure to the selected coordinates of the BACE.

In practice, it will be desirable to model a sufficient number of atoms of the BACE as defined by the coordinates of Table 1, which represent a binding pocket. Thus, in this embodiment of the invention, there will preferably be provided the coordinates of at least 5, preferably at least 10, more preferably at least 50 and even more preferably at least 100 and preferably 500 selected atoms of the BACE structure.

In order to provide a three-dimensional structure of compounds to be fitted to a BACE structure of the invention, the compound structure may be modelled in three dimensions using commercially available software for this purpose or, if its crystal structure is available, the coordinates of the structure may be used to provide a representation of the compound for fitting to a BACE structure of the invention.

The step of providing the structure of a candidate modulator molecule may involve selecting the compound by computationally screening a database of compounds for interaction with the binding cavity or cavities. For example, a 3-D descriptor for the potential modulator may be derived, the descriptor including geometric and functional constraints derived from the architecture and chemical nature of the binding cavity or cavities. The descriptor may then be used to interrogate the compound database, a potential modulator being a compound that has a good match to the features of the descriptor. In effect, the descriptor is a type of virtual pharmacophore.

In any event, the determination of the three-dimensional structure of BACE provides a basis for the design of new and specific ligands for BACE. For example, knowing the three-dimensional structure of BACE, computer modelling programs may be used to design different molecules expected to interact with possible or confirmed binding cavities or other structural or functional features of BACE. Examples of this are discussed in Schneider, G.; Bohm, H. J. *Drug Discov.Today* **2002**, *7*, 64-70.

More specifically, the interaction of a compound with BACE can be examined through the use of computer modelling using a docking program such as GOLD (Jones et al., *J. Mol. Biol.*, 245, 43-53 (1995), Jones et al., *J. Mol. Biol.,* 267, 727-748 (1997)), GRAMM (Vakser, I.A., *Proteins* , Suppl., 1:226-230 (1997)), DOCK (Kuntz et al, *J.Mol.Biol.* **1982** , *161*, 269-288, Makino et al, *J.Comput.Chem.* **1997**, *18*, 1812-1825), AUTODOCK

(Goodsell et al, *Proteins* **1990**, *8*, 195-202, Morris et al, *J.Comput.Chem.* **1998**, *19*, 1639-1662.), FlexX, (Rarey et al, *J.Mol.Biol.* **1996**, *261*, 470-489) or ICM (Abagyan et al, *J.Comput.Chem.* **1994**, *15*, 488-506). This procedure can include computer fitting of compounds to BACE to ascertain how well the shape and the chemical structure of the compound will bind to the BACE.

Also computer-assisted, manual examination of the binding site structure of BACE may be performed. The use of programs such as GRID (Goodford, *J. Med. Chem.*, 28, (1985), 849-857) - a program that determines probable interaction sites between molecules with various functional groups and an enzyme surface - may also be used to analyse the binding cavity or cavities to predict partial structures of inhibiting compounds.

Computer programs can be employed to estimate the attraction, repulsion, and steric hindrance of the two binding partners (i.e. the BACE and a candidiate modulator). Generally the tighter the fit, the fewer the steric hindrances, and the greater the attractive forces, the more potent the potential modulator since these properties are consistent with a tighter binding constant. Furthermore, the more specificity in the design of a potential drug, the more likely it is that the drug will not interact with other proteins as well. This will tend to minimise potential side-effects due to unwanted interactions with other proteins.

In another aspect, the present invention provides a method for identifying an agent compound (e.g. an inhibitor) which modulates BACE activity, comprising the steps of: (a) employing three-dimensional atomic coordinate data according to Table 1 to characterise at least one BACE binding site and preferably a plurality of BACE binding sites; (b) providing the structure of a candidate agent compound; (c) fitting the candidate agent compound to the binding sites; and (d) selecting the candidate agent compound.

Preferably sufficient binding sites are characterised to define a BACE binding cavity or cavities.

A plurality (for example two, three or four) of (typically spaced) BACE binding sites may be characterised and a plurality of respective compounds designed or selected. The agent compound may then be formed by linking the respective compounds into a larger compound which preferably maintains the relative positions and orientations of the respective compounds at the binding sites. The larger compound may be formed as a real molecule or by computer modelling.

In one embodiment a plurality of candidate agent compounds are screened or interrogated for interaction with the binding sites. In one example, step (b) involves providing the structures of the candidate agent compounds, each of which is then fitted in step (c) to computationally screen a database of compounds (such as the Cambridge Structural Database) for interaction with the binding sites, i.e. the candidate agent compound may be selected by computationally screening a database of compounds for interaction with the binding sites (see Martin, *J. Med. Chem.*, vol 35, 2145-2154 (1992)). In another example, a 3-D descriptor for the agent compound is derived, the descriptor including e.g. geometric and functional constraints derived from the architecture and chemical nature of the binding cavity or cavities. The descriptor may then be used to interrogate the compound database, the identified agent compound being the compound which matches with the features of the descriptor. In effect, the descriptor is a type of virtual pharmacophore.

In a related aspect, the present invention provides a method for identifying a candidate modulator (e.g. potential inhibitor) of BACE comprising the steps of: (a) employing a three-dimensional structure of BACE, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one BACE binding cavity, the three-dimensional structure being defined by atomic coordinate data according to Table 1; and (b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

Detailed structural information can then be obtained about the binding of the compound to BACE, and in the light of this information adjustments can be made to the structure or functionality of the compound, e.g. to improve its interaction with BACE. The above steps may be repeated and re-repeated as necessary.

K. Compound selection

In another aspect, in place of *in silico* methods, high throughput screening of compounds to select compounds with binding activity may be undertaken, and those compounds which show binding activity may be selected as possible candidate modulators, and further crystallized with BACE (e.g. by co-crystallization or by soaking) for X-ray analysis. The resulting X-ray structure may be compared with that of Table 1 for a variety of purposes.

L. Compounds of the invention

Having designed or selected possible binding candidate modulators (e.g. by *in silico* analysis, "wet" chemical methods, X-ray analysis etc.) by determining those which have favourable fitting properties (e.g. strong attraction between candidate and BACE), these can then be screened for activity.

Consequently all the methods of compound design and identification outlined above can optionally include the step of: (a) obtaining or synthesising the candidate modulator; and (b) contacting the candidate modulator with BACE to determine the ability of the candidate modulator to interact with BACE.

More preferably, in the latter step the candidate modulator is contacted with BACE under conditions to determine its function.

For example, in the contacting step above the candidate modulator is contacted with BACE in the presence of a substrate, and typically a buffer, to determine the ability of said candidate modulator to inhibit BACE. The substrate may be e.g. APP. So, for example, an assay mixture for BACE may be produced which comprises the candidate modulator, substrate and buffer.

Detailed structural information can be obtained about the binding of the candidate modulator to BACE, and in the light of this information adjustments can be made to the structure or functionality of the candidate modulator, e.g. to improve binding to the binding cavity or cavities. The above steps may be repeated and re-repeated as necessary.

Following identification of such compounds, it may be manufactured and/or used in the preparation, i.e. manufacture or formulation, of a composition such as a medicament, pharmaceutical composition or drug. These may be administered to individuals.

Thus, the present invention extends in various aspects not only to a compound as provided by the invention, but also a pharmaceutical composition, medicament, drug or other composition comprising such a compound e.g. for treatment (which may include preventative treatment) of disease; a method comprising administration of such a composition to a patient, e.g. for treatment of disease; use of such an inhibitor in the manufacture of a composition for administration, e.g. for treatment of disease; and a method

of making a pharmaceutical composition comprising admixing such an inhibitor with a pharmaceutically acceptable excipient, vehicle or carrier, and optionally other ingredients.

Thus a further aspect of the present invention provides a method for preparing a medicament, pharmaceutical composition or drug, the method comprising:

(a) identifying a BACE modulator molecule (which may thus be termed a lead compound) by a method of any one of the other aspects of the invention disclosed herein; (b) optimising the structure of the modulator molecule; and (c) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

The above-described processes of the invention may be iterated in that the modified compound may itself be the basis for further compound design.

By "optimising the structure" we mean e.g. adding molecular scaffolding, adding or varying functional groups, or connecting the molecule with other molecules (e.g. using a fragment linking approach) such that the chemical structure of the modulator molecule is changed while its original modulating functionality is maintained or enhanced. Such optimisation is regularly undertaken during drug development programmes to e.g. enhance potency, promote pharmacological acceptability, increase chemical stability etc. of lead compounds.

Modification will be those conventional in the art known to the skilled medicinal chemist, and will include, for example, substitutions or removal of groups containing residues which interact with the amino acid side chain groups of a BACE structure of the invention. For example, the replacements may include the addition or removal of groups in order to decrease or increase the charge of a group in a test compound, the replacement of a charge group with a group of the opposite charge, or the replacement of a hydrophobic group with a hydrophilic group or vice versa. It will be understood that these are only examples of the type of substitutions considered by medicinal chemists in the development of new pharmaceutical compounds and other modifications may be made, depending upon the nature of the starting compound and its activity.

Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural)

administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975.

Compositions may be used, e.g. for treatment (which may include preventative treatment) of a disease such as Alzheimer's disease or Alzheimer's-type pathology in Downs syndrome. Thus the invention provides a method comprising administration of such a composition to a patient, e.g. for treatment of a disease such as Alzheimer's disease; use of such an agent compound in the manufacture of a composition for administration, e.g. for treatment of a disease such as Alzheimer's disease; and a method of making a pharmaceutical composition comprising admixing such an agent compound with a pharmaceutically acceptable excipient, vehicle or carrier, and optionally other ingredients.

Exemplification

The invention will now be described with reference to specific Examples. These are merely exemplary and for illustrative purposes only: they are not intended to be limiting in any way to the scope of the invention described. These examples constitute the best mode currently contemplated for practicing the invention.

BACE protease was expressed at high levels in bacterial cells as insoluble inclusion bodies. To prepare functional protein for enzyme assay and structural studies these inclusion bodies were solublised using denaturants; the slow removal of these denaturants allowed the formation of the correct tertiary structure. In the method described here, BACE was expressed as a pro-sequence and required activation by a protease before becoming fully functional. Clostripain was used as an activating protease but produced multiple species of BACE as determined by mass spectrometry. In order to obtain a uniform homogenous protein after activation by clostripain, a number of different constructs were produced. These constructs focused on the mutation of two undesireable clostripain cleavage sites (following residues R56 and R57).

Cloning of BACE WT and BACE N->Q

The full-length DNA coding sequence of BACE was cloned from human cerebellum and human dorsal root ganglion (DRG) cDNA by PCR using oligonucleotide primers based on the published BACE sequence (EMBL accession no. AF190725). The full-length template sequence was obtained by PCR amplification using the following primers: hBACE-sp1 and -ap1 were used for primary amplification, hBACE-sp2 and -ap2 for nested PCR.

The primers were as follows:

hBACE-sp1	5'-AGCTCCCTCTCCTGAGAAGCCACC-3' (SEQ ID NO:22)
hBACE-ap1	5'-CCACAGGTGCCATCTGTGTCTCC-3' (SEQ ID NO:23)
hBACE-sp2	5'-CACCAGCACCACCCAGACTTGG-3' (SEQ ID NO:24)
hBACE-ap2	5'-AACCACGGAGGTGTGGTCCAGG-3' (SEQ ID NO:25)

A cDNA construct encoding a modified BACE form was made as follows. A partial BACE cDNA fragment was amplified using the full-length BACE clone as a template with primers hBACE_EC(Bam-M-14)_FOR (5' - CGG GAT CCA TGG CGG GAG TGC TGC CTG CC - 3') and hBACE_EC(Bam-453)_REV (5' - CGG GAT CCT TAT GAC TCA TCT GTC TGT GGA ATG TTG TAG C - 3'). The resulting 1342 bp PCR fragment was subcloned in vector pCR2.1-TOPO using the TOPO TA cloning® kit (Invitrogen) according to the manufacturer's instructions. The inserts of several resulting clones were fully sequenced and a clone containing no PCR mistakes was selected. The insert of this clone was excised

from the pCR2.1-TOPO construct using the *Bam*HI restriction endonuclease and subcloned to vector pET11a (Novagen) linearized with *Bam*HI. The BACE coding sequence (BACE WT, SEQ ID 1) in the resulting clones was confirmed by sequence analysis and the resulting correct construct was named M-T7-RGSM(BACE14-453)/pET11a.

Plasmid M-T7-RGSM(BACE14-453)/pET11a encodes a 455 amino acid residue protein named BACE WT containing a T7 epitope tag encoded by the pET11a vector sequence (AA 1 to 11), a linker sequence (AA 12-15; RGSM) and the partial BACE amino acid sequence from residue 14 to 453 (AA 16 to 455)(numbering based on SEQ ID 2). The calculated molecular mass of the resulting protein is 50.2 kDa.

The insert from construct Plasmid M-T7-RGSM(BACE14-453)/pET11a was amplified by PCR to incorporate a His_6 tag (CAT CAC CAT CAT CAC CAC) just upstream of the stop codon and *Bam*H1 site. Following cloning of this amplified fragment back into the original expression vector, the asparagine residues at positions -153, -172, -223 and –354 (numbers refer to the database BACE sequence BACE_HUMAN, P56817 in Swissprot) were mutated to glutamine (AAC to CAA) using the Quikchange™ mutagenesis system (Stratagene, used according to the manufacturers instructions), to generate BACE N->Q (SEQ ID 3).

Introduction of Activation Site Mutations

BACE WT and BACE N->Q, described above, were mutated using the Quickchange™ site directed mutagenesis protocol (Stratagene). Two complimentary oligonucleotides were designed which spanned the site of the mutation and which incorporated the amino acids changes to be made. These oligonucleotides were then used as primers in a PCR reaction producing each of the strands of the plasmid with the mutation present; the parental plasmid is digested with the methylation sensitive restriction endonuclease *Dpn*I and then transformed into competent *E.coli* cells.

Primers were applicable for the mutation of both BACE WT and BACE N->Q due to their high sequence homology. Seven constructs were produced; these are detailed below with the oligonucleotide sequence used to make the constructs.

1) BACE WT mutating arginine 56 to lysine and arginine 57 to lysine (SEQ ID 5)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO:26)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO:27)

2) BACE WT mutating arginine 57 to lysine (SEQ ID 7)

5' – CCCGAGGAGCCCGGCCGGAAGGGCAGCTTTGTGGAGATGG – 3' (SEQ ID NO:28)

5' – CCATCTCCACAAAGCTGCCCTTCCGGCCGGGCTCCTCGGG – 3' (SEQ ID NO:29)

3) BACE WT deleting arginine 57 (SEQ ID 9)

5' – CCCGAGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGAC – 3' (SEQ ID NO:30)

5' – GTCCACCATCTCCACAAAGCTGCCCCTGCCGGGCTCCTCGGG – 3' (SEQ ID NO:31)

4) BACE N->Q mutating arginine 56 to lysine and arginine 57 to lysine (SEQ ID 11)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO:32)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO:33)

5) BACE N->Q mutating arginine 57 to lysine (SEQ ID 15)

5' – CCCGAGGAGCCCGGCCGGAAGGGCAGCTTTGTGGAGATGG – 3' (SEQ ID NO:34)

5' – CCATCTCCACAAAGCTGCCCTTCCGGCCGGGCTCCTCGGG – 3' (SEQ ID NO:35)

6) BACE N->Q deleting arginine 57 (SEQ ID 17)

5' – CCCGAGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGAC – 3' (SEQ ID NO:36)

5' – GTCCACCATCTCCACAAAGCTGCCCCTGCCGGGCTCCTCGGG – 3' (SEQ ID NO:37)

7) BACE N->Q mutating arginine 56 to lysine and arginine 57 to lysine and removing the C terminal poly histidine tag (SEQ ID 13)

5' - CCCGAGGAGCCCGGCAAGAAGGGCAGCTTTGTGGAGATG – 3' (SEQ ID NO:38)

5' - CATCTCCACAAAGCTGCCCTTCTTGCCGGGCTCCTCGGG – 3' (SEQ ID NO:39)

5' – CCACAGACAGATGAGTCATGACACCATCATCACCACTAAG – 3' (SEQ ID NO:40)

5' – CTTAGTGGTGATGATGGTGTCATGACTCATCTGTCTGTGG – 3' (SEQ ID NO:41)

After transformation of the plasmid the protein coding region was checked by DNA sequencing.

Protein production (1)

Plasmid constructs were transformed into BLR(DE3) as follows: 1-2 µl DNA was added into 25ul BLR(DE3) competent cells. Cells were then heat shocked at 42°C for 45secs, followed by incubation for 30mins at 4°C . The sample was placed on ice for 2-3 mins before addition of 125-250ul HOC medium and left for 60 mins at 37°C. Cells were plated out onto agar containing carbenicillin & incubated at 37°C for 16h. Transformations were stored at 4°C. Transformed cells could be used up to after 8 weeks storage.

Colonies were inoculated in 100 ml LB broth with 1mM carbenicillin, and shaken for 16h at 25°C. 12 ml of this culture was added to 1 L of the same medium in baffle flasks. The typical total culture volume was 12, 20 or 24 L. Cells were induced by addition of 1mM IPTG at approximately OD_{600} 1.0. Cells were harvested 3 to 4 hours after induction by centrifugation for 7 min at 16 000 g. Cell pellets were resuspended in 1 litre TN buffer (150mM NaCl, 50mM Tris, pH 7.5) before addition of 10 mg lysozyme per litre of bacterial culture. The suspension was left for 20 mins under vigorous stirring then frozen at -70°C.

The lysates were thawed & adjusted to 1 mM MgCl2 and 20 µl 10 mg/ml DNAse, incubated 30-60 mins at 20°C, then 0.1 % Triton X-100 was added. Inclusion body washes were

performed in 11 wash steps, spun down at 13,000-16,000 g for 20mins at room temperature then resuspended by sonication in TNT buffer (TN buffer + 0.1% Triton 100). The washing step with TNT was repeated at least three times (up to seven times) until an almost homogenous dark cream precipitate was obtained. At this stage the pellet was washed twice with TN buffer. The typical yield for a 12 L culture of BACE WT constructs was 4.5 g washed inclusion body material.

Protein Refolding (1)

Each g of inclusion bodies was solubilised with 22.5 ml of 8 M urea, 50 mM Tris, 0.1 M beta-mercaptoethanol, 10 mM DTT, 1 mM EDTA. After 2 to 3 hours under gentle stirring, this was spun at 48 400 g for 25mins. This was then diluted 1 in 10 in 8 M Urea, 0.2 mM oxidized glutathione, 1.0 mM reduced glutathione. This is the starting solution for refolding

Refolding was accomplished by dilution into 20 volumes 20 mM Tris, 10 mM NDSB256 (3-(benzyldimethylammonio)propanesulfonate). The addition was achieved by slowly dripping from a burette into a strongly stirred solution. Addition was carried out at room temperature.

The pH was adjusted to approximately 9 using 13.5 ml 1 N HCl per 5 litre of refolding mix either immediately after dilution or 16 h after dilution. This was left at 4°C for 2-3 weeks. The refolding mix was then adjusted to pH 8.2 16h before concentrating. In instances where a longer incubation was applied it appeared that yields were slightly better. No precipitation was seen when attempting to refold BACE, even in totally unsuccessful conditions. Constructs BACE WT R57K, BACE WT R57DEL, BACE N->Q R57K, and BACE R57DEL refolded with lower yields.

Protein Purification of BACE from refolding step (1)

The refolded protein sample was concentrated by ultrafiltration using two parallel Vivaflow 200 cells (MWCO 30Kda), fed by a single pump. The concentration factor was not more than 200 times: if exceeded, precipitation occurred.

Concentrated refolded BACE was loaded and eluted on a 1.75 L Sephacryl 300 column run at a flow of 0.2 cm-1/min in 0.4 M Urea, 20 mM Tris, 10 mM HCl. Typical loading volume was 2% bed volume. From reconcentrated material three peaks are observed, the first one near the void volume (large aggregates), which merges into a second peak of aggregated

inactive material. The third peak (elutes at approx 40% of column volume) constitutes active BACE. For BACE WT constructs, the active fraction elutes at approximately 800ml.

Activation by Clostripain (1)

Clostripain (Cp; EC 3.4.22.8, from Worthington or Sigma C7403) was activated before use by solubilising the freeze dried material to 1.25 mg/ml in: 20 mM Calcium Acetate, 8 mM DTT, 100 mM Tris, pH 8 at 1.25 mg/ml 4 °C for at least 1h. The preparation was then stable at 4 °C for up to four weeks.

The third peak (typically 100 ml at an average of 0.3 mg ml) from Sephacryl 300 elution was treated with activated Cp, (1/100 dilution) for between 30-90mins at room temperature.

Activation of BACE WT R56KR57K, BACE N->Q R56KR57K & BACE N->Q R56KR57K no His by clostripain was performed as described above except that prior to activation the solution was concentrated ten fold using Vivaspin 20 ml 30 KDa MWCO.

The reaction was stopped by loading onto a Mono Q HR5-5 column equilibrated in 0.4 M Urea, 20 mM Tris, 10 mM HCl, 1 mM EDTA followed by washing using the same buffer. The protein was eluted with a 0 to 1 M NaCl gradient over 10 column volumes. A typical final yield of active soluble BACE WT R56KR57K is 1-2 mg of protein per litre of culture grown. The eluted protein was characterised and used in crystallisation assays.

Protein Production (2)

BLR (DE3) competent cells were transformed as described earlier and plated onto agar containing ampicillin (Amp). A colony was picked into 250ml LB + 100ug/ml Amp and grown overnight @ 37^{0}C, 185rpm. Following overnight growth (OD_{600} varied between 2.0-2.5) 10ml of this culture was used to inoculate 1L of fresh LB+100 μg/ml Amp in a 2L baffled flask. Routinely 24L of fresh LB+Amp would be inoculated from the overnight growth. Following inoculation, the 24L prep would be grown at 37^{0}C, 185rpm until an OD_{600} = 1.0 was obtained. Protein expression was induced by the addition of IPTG to a final concentration of 1mM. Cultures were incubated for a further 3 hours (at 37^{0}C, 185rpm) before harvesting by centrifugation at 8000 rpm for 10 mins (JLA 8.1000). Cell pellets could be stored at –80^{0}C or processed immediately.

All following protein production procedures were performed at room temperature unless stated otherwise. Cell pellet was re-suspended in 500ml of TN buffer (**TN buffer** – 150mM NaCl, 50mM Tris, pH7.5). 240mg of egg lysozyme (10mg/L of bacterial culture) was added to the re-suspended pellet. The suspension was left stirring for 20mins. Following this, 100ul of DNase 1 (10mg/ml stock) was added to the suspension and this was left stirring for 20mins. This lysate was clarified by centrifugation at 8000rpm for 20mins (JLA8.1000). The supernatant was discarded and the pellet was re-suspended in 100ml TNT buffer (**TNT buffer** – 150mM NaCl, 50mM Tris, pH7.5, 0.1% Triton X-100). Effort was made to break up any lumps present in the pellet so that a homogenous re-suspension was obtained. Following this, the re-suspension was sonicated for 2 mins (20 sec pulses). 400ml of TNT buffer was added to bring the volume of the suspension up to ~500mls. This was centrifuged for 20mins at 8000rpm and the supernatant discarded. The re-suspension in TNT buffer and sonication steps, as described above, were repeated twice. Following these three TNT washes, the pellet was re-suspended in 100ml of TN buffer and sonicated for 2 mins (20 second pulses). The suspension was centrifuged for 20 mins at 8000rpm. This wash in TN buffer was repeated once. Approximately 12-15g of inclusion bodies was obtained from the 24L of culture.

Protein Refolding (2)

The inclusion body preparation was solubilised by addition of 100mls of solubilisation buffer (**Sol. Buffer** – 8M urea, 50mM Tris, 0.1M beta-mercaptoethanol, 10mM DTT, 1mM EDTA). Effort was made to break up the inclusion body pellet using a pipette/spatula. The solution was left stirring gently overnight. The suspension was centrifuged for 30 mins at 25,000rpm (JA25). The supernatant (~100mls) was diluted by the addition of 900mls of 8M urea, 0.2mM oxidised glutathione, 1.0mM reduced glutathione.

The 1L of solubilised inclusion bodies as prepared above were refolded by a further 20x dilution. A 250ml aliquot of solubilised inclusion body prep was added drop-wise to 4.75L of refolding buffer (**Refolding buffer** – 20mM Tris, 10mM NDSB256 (3-(benzyldimethylammonio)propanesulfonate). The 4.75L of refolding buffer was stirred vigorously (not foaming) and the 250mls of inclusion body prep was added using a peristaltic pump. Care was taken to add the 250mls at a fast drop rather than a continuous pour. The remaining 750mls of inclusion body prep was diluted in the same way (250mls into 4.75L of refolding buffer). The four 5L vessels were placed at 4^0C overnight.

Following overnight incubation at 4^0C, the pH of each 5L vessel was adjusted to pH9.0 by addition of conc HCl. The vessels were then placed back at 4^0C and left for 3 weeks.

Protein Purification of BACE from Refolding Step (2)

Two parallel Vivaflow 200 cells (MWCO 30Kda) fed by a single peristaltic pump were used. Each 5L of refolding mix was concentrated to ~50mls. Over concentrating leads to precipitation and should be avoided. The concentration of 5L of refolding mix took ~2 hours. The 50mls of concentrated refolding mix was centrifuged for 25 mins, at 25,000rpm. The supernatant was then ready for gel filtration using a Sephacryl S-300 column (100x3.5). This method is limited by the volume of concentrated refolding mix than can be loaded onto the gel filtration column (50mls) per run. Sephacryl S-300 column was equilibrated with 0.4M urea, 20mM Tris, 10mM HCl (at a flow rate of 4ml/min). 50ml of sample can be loaded per run. The column was run at a flow rate of 4ml/min. SDS PAGE analysis of peaks 1,2 and 3 showed the presence of BACE (50Kda band) however activity assay of all three peaks showed only active BACE in peak 3. Fractions from Peak 3 were pooled and kept on ice.

Activation by Clostripain (2)

Clostripain (Sigma C7403) was prepared by dissolving protein to a final concentration of 1.25mg/ml in 20mM Calcium acetate, 8mM DTT, 100mM Tris pH 8.0. The clostripain was activated by incubating on ice for 1 hour prior to use.

Pooled fractions from peak 3 (~100ml at 0.2mg/ml) were activated by the addition of 1/100 dilution of 1.25mg/ml clostripain. The reaction was incubated at 37^0C in a water bath for 90 minutes. The reaction was stopped by addition of 1mM EDTA and placed on ice. **Note**: With each fresh batch of Sigma Clostripain, a time trial was performed on a small amount of BACE to verify the length of incubation needed at 37^0C. The length of incubation varied from 30-90 mins. Analysis by SDS PAGE clearly showed the appearance of the lower molecular weight activated species (~47Kda) from the larger inactivated species (~50Kda).

A Mono Q 5/5 ion exchange column was pre-equilibrated in 0.4M urea, 20mM Tris, 10mM HCl. The activated BACE (~50mls at ~0.2mg/ml) was loaded onto the Mono Q column at a flow rate of 1.0ml/min. Activated BACE was purified by applying a linear salt gradient (0.4M urea, 20mM Tris, 10mM HCl, 1.0M NaCl) over 20 column volumes. Following analysis by SDS PAGE and subsequent activity assay, fractions corresponding to activated

BACE were pooled and buffer exchanged into crystallisation buffer (20mM Tris, pH8.2, 150mM NaCl, 1mM DTT).

Protein Purification of BACE from Refolding Step (3)

By using method 3 in conjunction with the S-200 INDEX gel filtration column, all 20L of refolding mix could be processed in one go.

A Sartocon filtration cassette (MWCO 30Kda) was used in conjunction with a Watson Marlow 623S high speed pump. This assembly was set up as described in the manufactures operation manual. The 20L of refolding mix was concentrated down to ~500mls in less than 1 hour. Due to the dead volume in the assembly tubing, the volume could not be reduced further. At this stage the 500mls of concentrated refolding mix was filtered using a 0.2um filter. The filtered sample was then ready for gel filtration using an S-200 INDEX gel filtration column (100x10.0). A S-200 INDEX column pre-equilibrated in 0.4M urea, 20mm Tris, 10mM HCl was used. The column run was at a flow rate of 10mls/min.

SDS analysis of peaks 1,2 and 3 showed that BACE was present in all fractions. Activity assay showed that only peak 3 contain some BACE activity. Fractions from peak 3 were pooled (~250mls at 0.1mg/ml).

Prior to clostripain activation, the BACE sample was concentrated using a Resource Q ion exchange column. A 6/1 Resource Q column was pre-equilibrated in 0.4M urea, 20mM Tris, 10mM HCl. The Bace sample was loaded onto the column at 7ml/min. BACE was eluted off the column using a linear salt gradient (0.4M urea, 20mM Tris, 10mM HCl, 1M NaCl) over 5 column volumes. This step has the effect of dramatically reducing the sample volume size. Prior to clostripain activation, the protein sample is diluted with 0.4M urea, 20mM Tris, 10mM HCl to reduce the salt concentration to enable further purification using Mono Q. A dilution factor of 5:1 has been used successfully.

This is then followed by Clostripain Activation and Mono Q purification as outlined above.

Protein Characterization

The quality of the final preparation was evaluated by:

(a) SDS polyacrylamide gel electrophoresis, performed using commercial gels (Novagen) followed by Coomassie Brilliant Blue staining according to the manufacturer's instructions.

The purity as estimated by scanning a digital image of a gel was estimated to be at least 95%.

(b) Mass Spectroscopy: The eluted peak(s) were analysed using ESI-TOF-MS. Mass spectroscopy was performed using a Bruker "BioTOF" electrospray time of flight instrument. Samples were either diluted by a factor of 1000 straight from storage buffer into methanol/water/formic acid (50:48:2 v/v/v), or subjected to reverse phase HPLC separation using a C4 column. Calibration was achieved using Bombesin and angiotensin I using the 2+ and 1+ charged states. Data were acquired between 200 and 2000*m/z* range and were subsequently processed using Bruker's X-mass program. Mass accuracy was typically below 1 in 10 000.

MS Analysis of BACE WT R56KR57K (SEQ ID NO:6)

Full-length protein: MASMTGGQQMGRGSMAGVLPAHGT…

Predicted mass of full-length protein: 50147

Cleavage position:

MASMTGGQQMGR ↓ GSMAGVLPAHGT…

Predicted mass of BACE protein: 48911. This is the first intermediate fragment and is obtained very quickly and can be obtained as a stable fragment at lower enzyme concentration.

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓ LPRETDEEP…

Predicted mass of BACE protein: 45781. This is the final fragment obtained in the conditions described above. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 45783. The fragment typically elutes as a single peak from the Mono Q 5.5.

Mass Spec Analysis of BACE N->Q R56KR57K (SEQ ID NO:12)

Predicted mass of full-length protein: 50895

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓
LPRETDEEP…

Predicted mass of BACE protein: 46660.65. This is the final fragment obtained in the conditions described above. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 46655. The fragment typically elutes as two peaks from the Mono Q 5.5, the first corresponding to the desired fragment.

Mass Spec Analysis of BACE N->Q R56KR57K no His (SEQ ID NO:14)

Predicted mass of full-length protein: 50072.73

Cleavage position:

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLR ↓
LPRETDEEP…

Predicted mass of BACE protein: 45837.80. This is the first intermediate fragment, obtained rapidly between 30-60 minutes post activation and is suitable for crystallisation. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 45838.30. Typically elutes as 2 peaks from the Mono Q 5.5, the first peak corresponding to the desired fragment.

Cleavage position:
MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEE
PGK ↓ KGSFVEMV…

Predicted fragment mass: 44230.11. Further digestion beyond 60 minutes promotes the formation of the above fragment, not suitable for crystallisation. Observed ES-MS spectra of this fragment deconvolutes to a parent mass of 44228.03. This typically elutes as peak 2 from the Mono Q 5.5.

Method for Determining Activity of BACE

A fluorimetric assay was used to measure the activity of the refolded proteins. Activity of the BACE enzyme was measured using the fluorescent peptide R-E(EDANS)-E-V-N-L-*D-A-E-F-K(DABCYL)-R-OH (Bachem) as substrate. Assays were carried out in 96-well

black, flat-bottomed Cliniplates in a final assay volume of 100ul. The reaction rate was monitored at room temperature on a Fluoroskan Ascent plate reader with excitation and emission wavelengths of 355nm and 530nm respectively.

To determine the pH profile for the enzyme 8 nM BACE was incubated with 10 μM substrate in 50 mM sodium acetate (pH 3.5-5.5) or MES (pH 5.5-6.5) buffers at varying pHs and 5 % DMSO.

For kinetic characterization of the enzyme 8 nM BACE enzyme was incubated with varying concentrations of the substrate (2.5 – 80 μM) in 50 mM sodium acetate, pH 5, 5 % DMSO and the reaction monitored as described above. Kinetic parameters were determined by the standard Michaelis-Menten equation, using Prizm (GraphPad) software. 1mM OM 99 completely inhibits activity.

Protein Crystallisation

The sample of BACE was buffer exchanged into 20 mM Tris.HCl pH8.2, 150 mM NaCl, 1 mM DTT and concentrated down to approximately 7 mg/ml as determined by its theoretical extinction coefficient. Prior to crystallisation, the sample was spun at 55,000 rpm for 30 min using a Beckman benchtop ultracentrifuge. DMSO was added to a final concentration of 3 % (v/v).

Crystals of BACE from BACE WT R56KR57K, BACE N->Q R56KR57K & BACE N->Q R56KR57K no His were obtained by the hanging-vapour diffusion method at 20 °C using 1.5 μl of protein and an equivalent volume of reservoir solution. The reservoir solution contained 20-24 % PEG 5000 MME, 180-220 mM (e.g. 200 mM) ammonium iodide, 180-220 mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6). In an alternative, the reservoir solution may additionally contain 2.5% v/v glycerol.

Diffraction quality single crystals of BACE WT R56KR57K were obtained by the hanging-vapour diffusion method at 20 °C using 1.5 μl of protein and an equivalent volume of reservoir solution. The reservoir solution contained 20-22.5 % PEG 5000 MME, 180-220 mM (e.g. 200 mM) ammonium iodide, 180-220 mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6).

Crystals appear within the first week and grow to maximum dimensions within 14 days. The crystals were hexagonal rods with approximate dimensions of 0.2 x 0.05 x 0.05 mm.

They belonged to the hexagonal space group $P6_122$ with cell parameters a = b = 103.2 Å, c = 169.1 Å and accommodate one enzyme molecule per asymmetric unit, and a solvent content of 66 %.

Inhibitor Soaking

BACE inhibitors were dissolved in DMSO to a concentration of 500 mM and then diluted 1 in 10 in a harvesting solution composed of 220 mM ammonium iodide, 220 mM sodium cacodylate pH 6.4 and 22% PEG 5K MME or 100-200 mM sodium citrate pH 5.0, 200 mM ammonium iodide and 30% PEG 5K MME. Apo-BACE protein crystals were transferred into the harvesting solution for a period of up to 24 hours prior to being dipped in cryoprotectant (20% PEG 5000 MME, 200 mM ammonium iodide, 200 mM sodium cacodylate pH 6.4 and 20% $_{(v/v)}$ glycerol or 200 mM sodium citrate pH 5.0, 200 mM ammonium iodide, 30% PEG 5K MME and 20% $_{(v/v)}$ glycerol) containing the inhibitor and frozen in liquid nitrogen.

Data Collection & Processing

The structure of apo-BACE was solved from BACE WT R56KR57K to 1.75 Å resolution using the method of molecular replacement. Prior to data collection, crystals were exposed, briefly, to cryoprotectant, described previously, before flash freezing. Data was collected at 100 °K on beamline ID14-1 at the European Synchrotron Radiation Facility using an ADSC Quantum4 CCD detector, with a wavelength of 0.934Å and processed using MOSFLM (Leslie, A. G. W. (1992). In *Joint CCP4 and EESF-EACMB Newsletter on Protein Crystallography*, vol. 26, Warrington, Daresbury Laboratory). The dataset was scaled using SCALA (CCP4 – Collaborative Computational Project 4. (1994) The CCP4 Suite: Programs for Protein Crystallography. *Acta Crystallographica* D50, 760-763) and the intensities converted to structure factor amplitudes with TRUNCATE (Evans, P. R. (1997). Scaling of MAD data. In *Recent Advances in Phasing* (ed. K. S. Wilson, G. Davies, A. W. Ashton and S. Bailey), pp. 97-102. Council for the Central Laboratory of the Research Councils Daresbury Laboratory, Daresbury, UK), from the CCP4 suite of programs (CCP4 – Collaborative Computational Project 4. (1994) The CCP4 Suite: Programs for Protein Crystallography. *Acta Crystallographica* D50, 760-763). Statistics for the processing are shown in Table 2.

TABLE 2: Data collection statistics for apo-BACE.

Resolution	1.75 Å
Mosaicity	0.34°
Completeness	95.9 %
Multiplicity	6.3
Rmerge	0.097

Structure Determination and Refinement

The structure of apo-BACE was solved by molecular replacement using the program EPMR (Kissinger CR, Gehlhaar DK, Fogel DB, Acta Crystallogr D Biol Crystallogr, 1999,vol 55 (Pt 2), 484-91). Initially, it was impossible to know whether the correct space group was $P6_122$ or $P6_522$, therefore molecular replacement attempts were performed against both. Default parameters and a resolution range of 15–4Å were used in conjunction with the A chain of 1FKN (Hong et al, 2000) as the search model. A solution was found for $P6_122$ with an Rfactor of 0.458 and a correlation coefficient of 0.543. In an attempt to reduce model bias, the molecular replacement solution was used as the starting point for ARP/wARP (Morris RJ, Perrakis A, Lamzin VS, Acta Crystallogr D Biol Crystallogr, 2002,vol 58,(Pt 6 No 2), 968-75) to perform automated backbone tracing using warpNtrace and side chain building via the Side_dock procedure. This produced a discontinuous model composed of 244 out of 385 residues spanning 12 amino acid chains. Cycles of structural refinement with REFMAC5 (Murshudov, G. N., Vagin, A. A. and Dodson, E. J. (1997). Refinement of macromolecular structures by the maximum-likelihood method. *Acta Crystallographica*, 1997 D53, 240-255) were alternated with manual rebuilding of the model using QUANTA (Jones et al., Acta Crystallography A47 (1991), 110-119 and commercially available from Accelerys, San Diego, CA). The model was extended to 329 residues with chain breaks between 156-170, 255-280 and 311-325. CNX (Brunger et al., *Current Opinion in Structural Biology*, Vol. 8, Issue 5, October 1998, 606-611, and commercially available from Accelerys, San Diego, CA) composite omit maps were

generated to allow further building of the structure and finally water molecules added using DenInt (Astex internal software library). Refinement statistics are shown in Table 3.

TABLE 3: Final refinement statistics for apo-BACE

Rwork	0.251
Rfree	0.284
RMS bond deviation from ideality	0.011
RMS bond angle deviation from ideality	1.30
Average Bfactor for structure	32.99

This data indicates that the final structure is of good quality; the Rfactors indicating that the refined model has a good agreement with the experimental data. The RMS deviations from ideality indicate that the geometry of the model is good.

Description of the Apo Structure of BACE

The structure of BACE we present here has been solved in the absence of substrate or inhibitor. This is the first time that such a structure has been described. The solution of this structure has been possible as we have, for the first time, crystallized BACE without compound in a form suitable for diffracting X-rays, and hence allowed the determination of the apo structure of BACE. Under our conditions it crystallizes in space group $P6_122$ with a monomer in the asymmetric unit. This is a novel crystal form of BACE.

The protein chain has been traced in the electron density from residue Phe47p to Ala157, and then from Ala168 to Asn385. There is no indication as to the position of residues 158 to 167 in the electron density map. In addition to the protein atoms, the model contains 3 iodine atoms and 285 water molecules in its present state of refinement.

The majority of the residues in this form of BACE are well defined, the exceptions being some exposed residues. Parts of the protein surface are exposed to solvent, as a consequence of the molecular packing within the crystal lattice (Figure 1). Residues 255-259, 271-277 and 310 to 317 are exposed and have high B-factors relative to the body of the protein. In

addition, residues 304 to 309 pack against an exposed loop and are poorly ordered with high b-factors. There are three disulphide bonds in BACE, two of these are well defined in the electron density, the third, between Cys269 and Cys319 has high temperature factors. This is probably a consequence of its proximity to exposed parts of the protein.

BACE as it has been solved in this form, is a compact globular protein, which is formed by two domains; domain 1 being comprised of residues 47p-146 and domain 2 of residues (146-385)(numbering from Hong *et al*, 2000). The active site lies between these two domains, and contains the two conserved aspartic acid residues, Asp32 and Asp228, which define the active sites of aspartic proteinases. In our structure, a single water molecule is coordinated between these two residues.

The overall fold of the protein is similar to that of 1FKN (Hong et al, 2000), with a few minor, but potentially significant changes. Residues 158-166 are ordered in the structure of BACE in the presence of OM99-2 (in the $P2_1$ form), and consist of a loop plus a short helix. In the $P6_122$ unliganded form, these residues cannot be seen, and are assumed to be mobile. This may be a consequence of the crystal packing arrangement in this form. Residues 69-75 have a different arrangement in the crystal form described here, to their arrangement in the crystal structure of the OM99-2 complex. The residues are displaced upward relative to the active site in the structure without OM99-2. The two molecules can be superposed over all residues using the program MAPS (MAPS-Multiple Alignment of Proteins Structures Version 0.2, Sep-7-1999, Guoguang, Lund University, Sweden and Lu, G. An Approach for Multiple Alignment of Protein Structures (1998, in manuscript) to give an r.m.s.d. of 0.74 Å. This results in close alignment of the N-terminal residue prior to residue 69 and subsequent to 75. In contrast the CA atoms of residue 71 are displaced by 3.3 Å, those of residue 72 by 4.3 Å, and those of residue 73 by 6.0 Å. (Figure 2) The reason for this difference is postulated to be the interaction of OM99-2 backbone residues with the protein residues, in an arrangement analogous to a beta sheet. This interaction pulls the loop down over the substrate in the active site, and locks it in position. In the absence of substrate, or peptidic inhibitor, the loop moves back up again.

In addition to these local changes in structure, on binding of inhibitor, there appears to be a slight shift in the domain positions relative to each other, resulting in an average difference in position in the C-terminal domain CA atoms of about 2.0 Å, when the molecules are superposed using the N-terminal CA atoms.

The symmetry of the $P6_122$ crystal system has resulted in a packing arrangement which brings part of a symmetry related molecule very close to the active site entrance of BACE. Gln73 from a symmetry related molecule lies very close to the entrance to the active site of BACE in this crystal form, and overlaps with the position occupied by P4 Glu in OM99-2. However, this does not interfere with the usefulness of this crystal system to soak in inhibitors, as we have shown that these crystals can be used to soak BACE inhibitors into the active site.

Incorporation by Reference

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference. Particular reference is made to the references listed below:

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Equivalents

The foregoing description details presently preferred embodiments of the present invention which are therefore to be considered in all respects as illustrative and not restrictive. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents, modifications and variations to the specific embodiments of the invention described specifically herein. Such equivalents, modifications and variations are intended to be (or are) encompassed in the scope of the following paragraphs:

1. A mutant BACE protein, which protein lacks one or more proteolytic cleavage sites recognized by clostripain (or another protease which recognizes the same cleavage site as clostripain).

2. The protein of paragraph 1 wherein BACE residues R56 and/or R57 (based on numbering of SwissProt P56817) are mutated or deleted.

3. The protein of paragraph 2 wherein R56 or R57 are mutated by the substitution of arginine for lysine.

4. The protein of paragraph 2 wherein R56 and R57 are mutated by the substitution of arginine for lysine.

5. The protein of any one of the preceding paragraphs which comprises BACE residues 56 to 396 (based on numbering of SwissProt P56817).

6. A mutant BACE protein (for example, a mutant BACE protein as defined in any one of the preceding paragraphs) which is truncated at the N-terminal up to and including R42, R45, G55, R56 or R57.

7. The protein of any one of paragraphs 1 to 6 truncated at the C-terminal such that at least residues 454 *et seq.* are absent.

8. The protein of paragraph 7 truncated at the C-terminal such that at least residues 447 *et seq.* are absent.

9. The protein of any one of the preceding paragraphs wherein the asparagine residues at positions 153, 172, 223 and 354 are mutated to glutamine residues.

10. The protein of any one of the preceding paragraphs which is un- or deglycolsylated.

11. A mutant BACE protein selected from: (a) SEQ ID 6; (b) SEQ ID 8; (c) SEQ ID 10; (d) SEQ ID 12; (e) SEQ ID 14; (f) SEQ ID 16; (g) SEQ ID 18; (h) SEQ ID 19; (i) SEQ ID 20; (j) SEQ ID 21.

12. Nucleic acid encoding the protein of any one of the preceding paragraphs.

13. A vector comprising the nucleic acid of paragraph 12.

14. A host cell comprising the vector of paragraph 13.

15. A process for producing the protein of any one of paragraphs 1 to 11 comprising the steps of: (a) culturing the host cell of paragraph 14 under conditions suitable for expression of the protein; and optionally (b) isolating the expressed recombinant BACE protein.

16. A process for producing refolded recombinant BACE comprising the steps of: (a) solubilising the recombinant BACE; (b) diluting the solubilised BACE into an aqueous buffer containing sulfobetaine (for example at a concentration of 10 to 50 mM); and (c) maintaining the diluted solution at low temperature (for example, 3 to 6°C) and at high pH (e.g. 9 to 10.5) for at least 2 weeks.

17. The process of paragraph 16 wherein the recombinant BACE is produced according to the process of paragraph 15.

18. Refolded recombinant BACE produced by, or obtainable by, the process of paragraph 16 or paragraph 17.

19. A process for producing a crystal of BACE comprising the step of refolding recombinant BACE protein according to the process of paragraph 16 or paragraph 17.

20. A process for producing a crystal of BACE comprising the step of growing the crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME (for example, 20-24 % PEG 5000 MME, e.g. 20-22.5 % PEG 5000 MME), 180-220 mM (e.g. 200 mM) ammonium iodide and 180-22- mM (e.g. 200 mM) tri-sodium citrate (pH 6.4-6.6).

21. The process of paragraph 20 wherein the BACE is recombinant and the process further comprises the preliminary step of refolding the recombinant BACE according to the process of paragraph 16 or paragraph 17.

22. The process of any one of paragraphs 18 to 20 further comprising the step of activating the BACE by clostripain digestion.

23. The process of paragraph 21 wherein the BACE is as defined in any one of paragraphs 1 to 10.

24. A crystal of BACE produced by, or obtainable by, the process of any one of paragraphs 18 to 22.

25. A crystal of BACE having a hexagonal space group $P6_122$.

26. The crystal of paragraph 25 having unit cell dimensions of a=b=103.2 Å, c=169.1 Å, $\alpha=\beta=60°$, $\gamma=120°$, and a unit cell variability of 5% in all dimensions.

27. The crystal of paragraph 25 or paragraph 26 which contains one copy of BACE in the asymmetric unit.

28. A crystal of BACE (e.g. a crystal according to any one of paragraphs 24 to 27) having a resolution better than 3 Å.

29. The crystal of paragraph 28 having a resolution better than 2.5 Å.

30. The crystal of paragraph 29 having a resolution better than 1.8 Å.

31. A crystal of BACE (e.g. a crystal according to any one of paragraphs 24 to 30) comprising a structure defined by all or a portion of the co-ordinates of Table 1.

32. The crystal of paragraph 31 comprising a structure defined by a portion of the coordinates of Table 1 which coordinates relate to: (a) the BACE catalytic domain; and/or (b) a BACE active site; and/or (c) a BACE binding cavity; and/or (d) selected amino acid residues of a BACE binding cavity located in a protein framework which holds the selected amino acids in a relative spatial configuration which corresponds to the spatial configuration of those amino acids in Table 1; and/or (d) a BACE binding site.

33. The crystal of paragraph 32 wherein the portion of the coordinates of Table 1 comprise (or consist essentially of) those relating to residues SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368 (based on the numbering of SwissProt P56817).

34. The crystal of paragraph 33 wherein the portion of the coordinates of Table 1 comprise (or consist essentially of) those relating to residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396 and ILE447 (based on the numbering of SwissProt P56817).

35. The crystal of any one of paragraphs 24 to 34 which is capable of being soaked with compound(s) to form co-complex structures.

36. The crystal of any one of paragraphs 24 to 35 which is soaked with one or more compound(s) to form co-complex structures.

37. The crystal of any one of paragraphs 24 to 36 wherein the BACE is co-crystallized with one or more compound(s) to form co-crystallized structures.

38. The crystal of any one of paragraphs 24 to 35 which is an apo crystal.

39. The crystal of any one of paragraphs 24 to 38 wherein the BACE is a wild-type BACE.

40. The crystal of paragraph 39 wherein the BACE is a human BACE.

41. The crystal of paragraph 40 wherein the BACE is a homologue of a human BACE.

42. The crystal of paragraph 41 wherein the homologue is an orthologue or a paralogue of a human BACE.

43. The crystal of any one of paragraphs 24 to 38 wherein the BACE is a mutant and/or recombinant BACE.

44. The crystal of paragraph 43 wherein the BACE: (a) lacks the BACE transmembrane and/or cytoplasmic domain(s); and/or (b) lacks one or more glycolsylation sites; and/or (c) comprises one or more peptide tags (for example a his tag); and/or (d) lacks one or more protease cleavage site(s); and/or (e) is truncated at the N-terminus; and/or (f) is truncated at the C-terminus; and/or (f) lacks the BACE pro-sequence.

45. The crystal of paragraph 44 wherein the BACE mutant lacks one or more clostripain cleavage sites.

46. The crystal of paragraph 45 wherein BACE residues R56 and/or R57 (based on numbering of SwissProt P56817) are mutated or deleted.

47. The crystal of paragraph 46 wherein R56 or R57 are mutated by the substitution of arginine for lysine.

48. The crystal of paragraph 46 wherein R56 and R57 are mutated by the substitution of arginine for lysine.

49. The crystal of any one of paragraphs 43 to 48 wherein the BACE mutant is truncated at the N-terminal up to and including R42.

50. The crystal of any one of paragraphs 43 to 49 wherein the BACE mutant is truncated at the C-terminal such that at least residues 396 *et seq.* are absent.

51. The crystal of paragraph 50 wherein the BACE mutant is truncated at the C-terminal such that at least residues 387 *et seq.* are absent.

52. The crystal of any one of paragraphs 43 to 51 wherein the asparagine residues at positions 153, 172, 223 and 354 of the BACE mutant are mutated to glutamine residues.

53. The crystal of any one of paragraphs 24 to 52 wherein the BACE is un- or deglycolsylated.

54. The crystal of paragraph 43 wherein the BACE mutant is selected from: (a) SEQ ID 19; (b) SEQ ID 20; (c) SEQ ID 21.

55. The process of any one of paragraphs 19 to 23 wherein the process produces a crystal of BACE as defined in any one of paragraphs 24 to 54.

56. A three-dimensional representation of BACE or of a portion of BACE, which representation comprises all or a portion of the coordinates of Table 1.

57. The three-dimensional representation of paragraph 56 which is a model constructed from all or a portion of the coordinates of Table 1.

58. The model of paragraph 57 wherein the portion of BACE is a BACE binding cavity and the portion of the coordinates of Table 1 comprise those of atoms defining a binding site within the binding cavity (for example, wherein the coordinates are as defined in paragraph 33 or paragraph 34).

59. A three-dimensional representation of a compound which fits the model of paragraph 57 or paragraph 58.

60. The three-dimensional representation of paragraph 59 which is a model of the compound.

61. The model of paragraph 60 wherein the compound is a pharmacophore.

62. The model of any one of paragraphs 57, 58, 60 or 61 which is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

63. The model of any one of paragraphs 57, 58, 60, 61 or 62 which is in physical form.

64. The model of any one of paragraphs 57, 58, 60, 61 or 62 which is in electronic form.

65. The model of paragraph 64 which comprises a graphical image display on a computer screen.

66. A computer-based method for the analysis of the interaction of a molecular structure with a BACE structure of the invention, which comprises: (a) providing a BACE model as defined in paragraph 57, 58 or 62 to 65; (b) providing a molecular structure to be fitted to said BACE model; and (c) fitting the molecular structure to the BACE model to produce a compound model as defined in paragraph 60, 61 or 62 to 65.

67. A computer-based method for the analysis of the interaction of a molecular structure with a BACE structure of the invention, which comprises: (a) providing the structure of a BACE as defined by the coordinates of Table 1; (b) providing a molecular structure to be fitted to said BACE structure; and (c) fitting the molecular structure to the BACE structure of Table 1.

68. A computer-based method for the analysis of molecular structures which comprises: (a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ("selected coordinates"); (b) providing the structure of a molecular structure to be fitted to the selected coordinates; and (c) fitting the structure to the selected coordinates of the BACE structure.

69. The method of paragraph 68 wherein the selected coordinates represent a binding pocket.

70. The method of paragraph 68 or paragraph 69 wherein the selected coordinates are of at least 5, 10, 50 or 100 atoms.

71. The method of paragraph 69 or paragraph 70 wherein the selected coordinates are as defined in paragraph 33 or paragraph 34.

72. A computer-based method of rational drug design comprising the method of any one of paragraphs 66 to 71.

73. A computer-based method of rational drug design comprising comprising: (a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ("selected coordinates"); (b) providing the structures of a plurality of molecular fragments; (c) fitting the structure of each of the molecular fragments to the selected coordinates; and (d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

74. A method for identifying a candidate modulator (e.g. candidate inhibitor) of BACE comprising the steps of: (a) employing a three-dimensional structure of BACE, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one BACE binding cavity, the three-dimensional structure being defined by atomic coordinate data according to Table 1; and (b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

75. The method of paragraph 74 wherein the three-dimensional structure of BACE is a model as defined in paragraph 57 or paragraph 58.

76. A method for identifying an agent compound (e.g. an inhibitor) which modulates BACE activity, comprising the steps of: (a) employing three-dimensional atomic coordinate data according to Table 1 to characterise at least one (e.g. a plurality of) BACE binding site(s); (b) providing the structure of a candidate agent compound; (c) fitting the candidate agent compound to the binding sites; and (d) selecting the candidate agent compound.

77. The method of paragraph 76 wherein in step (a) the three-dimensional atomic coordinate data are employed to create a model as defined in paragraph 57, 58 or 62 to 65.

78. The method of any one of paragraphs 73 to 77further comprising the step of: (a) obtaining or synthesising the candidate agent or modulator; and (b) contacting the

candidate modulator with BACE to determine the ability of the candidate modulator to interact with BACE.

79. A method of assessing the ability of a candidate modulator to interact with BACE which comprises the steps of: (a) obtaining or synthesising said candidate modulator; (b) forming a crystallized complex of BACE and said candidate modulator; and (c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said candidate modulator to interact with BACE.

80. A method for determining the structure of a compound bound to BACE, said method comprising: (a) mixing BACE with the compound to form a BACE-compound complex; (b) crystallizing the BACE-compound complex; and (c) determining the structure of said BACE-compound(s) complex by reference to the data of Table 1.

81. A method for determining the structure of a compound bound to BACE, said method comprising: (a) providing a crystal of BACE; (b) soaking the crystal with one or more compound(s) to form a complex; and (c) determining the structure of the complex by employing the data of Table 1.

82. A method of determining the three dimensional structure of a BACE homologue or analogue of unknown structure, the method comprising the steps of: (a) aligning a representation of an amino acid sequence of the BACE homologue or analogue with the amino acid sequence of the BACE of Table 1 to match homologous regions of the amino acid sequences; (b) modelling the structure of the matched homologous regions of said target BACE of unknown structure on the corresponding regions of the BACE structure as defined by Table 1; and (c) determining a conformation for the BACE homologue or analogue which substantially preserves the structure of said matched homologous regions.

83. The method of paragraph 82 wherein steps (a) and/or (b) and/or (c) are performed by computer modelling.

84. A method of providing data for generating structures and/or performing rational drug design for BACE, BACE homologues or analogues, complexes of BACE with a potential modulator, or complexes of BACE homologues or analogues with potential modulators, the method comprising: (i) establishing communication with a remote

device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE, at least one sub-domain of the three-dimensional structure of BACE, or the coordinates of a plurality of atoms of BACE; (b) structure factor data for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE homologue or analogue generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and (ii) receiving said computer-readable data from said remote device.

85. A computer system containing one or more of: (a) atomic coordinate data according to Table 1, said data defining the three-dimensional structure of BACE or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a target BACE protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

86. The computer system of paragraph 85 comprising: (i) a computer-readable data storage medium comprising data storage material encoded with the computer-readable data; (ii) a working memory for storing instructions for processing said computer-readable data; and (iii) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-readable data and thereby generating structures and/or performing rational drug design.

87. The computer system of paragraph 86 further comprising a display coupled to said central-processing unit for displaying said structures.

88. A computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion of the structure coordinates of BACE of Table 1, or a homologue of BACE, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms (nitrogen-carbon$_{\alpha}$-carbon) of Table 1 of not more than 1.5Å.

89. A computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for BACE according to Table 1; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

90. A computer readable medium with at least one of: (a) atomic coordinate data according to Table 1 recorded thereon, said data defining the three-dimensional structure of BACE, or at least selected coordinates thereof; (b) structure factor data for BACE recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1; (c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1; (d) atomic coordinate data of a BACE-ligand complex or a BACE homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

91. A method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1, and either (a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or (b) assigning NMR spectra Peaks of said protein by manipulating the coordinates of Table 1.

92. A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a BACE modulator molecule according to the

method as defined in any one of paragraphs 73 to 79; (b) optimising the structure of the modulator molecule; and (c) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

93. A medicament, pharmaceutical composition or drug produced by, or obtainable by, the process of paragraph 92.

94. A compound identified, produced or obtainable by the process or method of any one of paragraphs 73 to 79.

95. A pharmaceutical composition, medicament, drug or other composition comprising the compound of paragraph 94.

96. The medicament, pharmaceutical composition or drug of paragraph 93, compound of paragraph 94 or composition of paragraph 95 for use in medicine, for example for use in therapy or prophylaxis.

97. The medicament, pharmaceutical composition, drug or composition of paragraph 96 wherein the therapy or prophylaxis comprises inhibiting BACE or the production of Aβ or fragments thereof or the treatment of Alzheimer's disease.

98. A method of inhibiting BACE or the production of Aβ or fragments thereof or treating Alzheimer's disease comprising administering the medicament, pharmaceutical composition, drug or composition of paragraph 96 to the patient.

99. The method of paragraph 84, wherein the computer readable data is transmitted form the remove device.

100. The method of paragraph 99, wherein the data is transmitted electronically or optically.

TABLE 1

ATOM	1	N	PHE	A	47p	65.730	61.598	-17.857	1.00	56.68	A	N
ATOM	2	CA	PHE	A	47p	66.426	61.383	-16.552	1.00	54.16	A	C
ATOM	3	C	PHE	A	47p	67.801	60.738	-16.734	1.00	54.30	A	C
ATOM	4	O	PHE	A	47p	68.258	59.983	-15.869	1.00	52.46	A	O
ATOM	5	CB	PHE	A	47p	65.566	60.500	-15.635	1.00	54.61	A	C
ATOM	6	CG	PHE	A	47p	64.161	61.008	-15.429	1.00	54.65	A	C
ATOM	7	CD1	PHE	A	47p	63.110	60.508	-16.186	1.00	56.27	A	C
ATOM	8	CD2	PHE	A	47p	63.887	61.970	-14.463	1.00	55.01	A	C
ATOM	9	CE1	PHE	A	47p	61.812	60.972	-15.995	1.00	57.39	A	C
ATOM	10	CE2	PHE	A	47p	62.596	62.435	-14.266	1.00	56.06	A	C
ATOM	11	CZ	PHE	A	47p	61.556	61.938	-15.035	1.00	56.47	A	C
ATOM	12	N	VAL	A	48p	68.468	61.048	-17.845	1.00	54.26	A	N
ATOM	13	CA	VAL	A	48p	69.737	60.395	-18.200	1.00	54.45	A	C
ATOM	14	C	VAL	A	48p	70.910	60.742	-17.276	1.00	53.21	A	C
ATOM	15	O	VAL	A	48p	71.847	59.947	-17.128	1.00	56.35	A	O
ATOM	16	CB	VAL	A	48p	70.156	60.691	-19.662	1.00	57.43	A	C
ATOM	17	CG1	VAL	A	48p	69.222	59.972	-20.636	1.00	58.42	A	C
ATOM	18	CG2	VAL	A	48p	70.204	62.208	-19.944	1.00	57.43	A	C
ATOM	19	N	GLU	A	1	70.860	61.925	-16.668	1.00	49.17	A	N
ATOM	20	CA	GLU	A	1	71.845	62.329	-15.674	1.00	46.84	A	C
ATOM	21	C	GLU	A	1	71.857	61.373	-14.479	1.00	42.66	A	C
ATOM	22	O	GLU	A	1	72.901	61.125	-13.891	1.00	45.10	A	O
ATOM	23	CB	GLU	A	1	71.532	63.740	-15.171	1.00	48.32	A	C
ATOM	24	CG	GLU	A	1	70.180	64.053	-14.545	0.00	50.15	A	C
ATOM	25	CD	GLU	A	1	68.942	64.394	-15.351	0.00	51.10	A	C
ATOM	26	OE1	GLU	A	1	68.516	63.562	-16.178	0.00	51.29	A	O
ATOM	27	OE2	GLU	A	1	68.395	65.500	-15.155	0.00	51.61	A	O
ATOM	28	N	MET	A	2	70.685	60.855	-14.125	1.00	37.18	A	N
ATOM	29	CA	MET	A	2	70.525	60.001	-12.942	1.00	32.72	A	C
ATOM	30	C	MET	A	2	70.875	58.531	-13.154	1.00	29.50	A	C
ATOM	31	O	MET	A	2	71.014	57.787	-12.183	1.00	29.19	A	O
ATOM	32	CB	MET	A	2	69.099	60.111	-12.415	1.00	30.14	A	C
ATOM	33	CG	MET	A	2	68.733	61.514	-12.005	1.00	34.84	A	C
ATOM	34	SD	MET	A	2	67.103	61.723	-11.322	1.00	36.26	A	S
ATOM	35	CE	MET	A	2	66.607	63.243	-12.134	1.00	40.05	A	C
ATOM	36	N	VAL	A	3	71.008	58.079	-14.396	1.00	28.21	A	N
ATOM	37	CA	VAL	A	3	71.291	56.669	-14.611	1.00	29.18	A	C
ATOM	38	C	VAL	A	3	72.690	56.364	-14.085	1.00	27.28	A	C
ATOM	39	O	VAL	A	3	73.622	57.149	-14.298	1.00	28.33	A	O
ATOM	40	CB	VAL	A	3	71.137	56.248	-16.094	1.00	32.19	A	C
ATOM	41	CG1	VAL	A	3	71.649	54.826	-16.299	1.00	30.92	A	C
ATOM	42	CG2	VAL	A	3	69.667	56.353	-16.525	1.00	32.71	A	C
ATOM	43	N	ASP	A	4	72.803	55.254	-13.359	1.00	28.19	A	N
ATOM	44	CA	ASP	A	4	74.066	54.739	-12.825	1.00	29.50	A	C
ATOM	45	C	ASP	A	4	74.600	55.632	-11.703	1.00	27.86	A	C
ATOM	46	O	ASP	A	4	75.797	55.682	-11.454	1.00	28.77	A	O
ATOM	47	CB	ASP	A	4	75.107	54.575	-13.940	1.00	32.06	A	C
ATOM	48	CG	ASP	A	4	76.254	53.655	-13.553	1.00	37.52	A	C
ATOM	49	OD1	ASP	A	4	76.029	52.572	-12.945	1.00	38.24	A	O
ATOM	50	OD2	ASP	A	4	77.438	53.952	-13.829	1.00	45.15	A	O
ATOM	51	N	ASN	A	5	73.694	56.308	-11.015	1.00	24.98	A	N
ATOM	52	CA	ASN	A	5	74.062	57.172	-9.876	1.00	18.95	A	C
ATOM	53	C	ASN	A	5	74.270	56.415	-8.544	1.00	22.40	A	C
ATOM	54	O	ASN	A	5	74.564	57.045	-7.515	1.00	21.31	A	O
ATOM	55	CB	ASN	A	5	73.064	58.329	-9.718	1.00	21.03	A	C
ATOM	56	CG	ASN	A	5	71.677	57.870	-9.366	1.00	16.73	A	C
ATOM	57	OD1	ASN	A	5	71.424	56.673	-9.325	1.00	19.74	A	O
ATOM	58	ND2	ASN	A	5	70.801	58.808	-9.035	1.00	21.06	A	N
ATOM	59	N	LEU	A	6	74.099	55.098	-8.562	1.00	15.94	A	N
ATOM	60	CA	LEU	A	6	74.323	54.236	-7.397	1.00	16.57	A	C
ATOM	61	C	LEU	A	6	75.531	53.321	-7.510	1.00	21.72	A	C
ATOM	62	O	LEU	A	6	75.855	52.780	-8.581	1.00	21.55	A	O
ATOM	63	CB	LEU	A	6	73.109	53.352	-7.078	1.00	18.17	A	C
ATOM	64	CG	LEU	A	6	71.707	53.957	-6.866	1.00	19.32	A	C
ATOM	65	CD1	LEU	A	6	70.695	52.916	-6.521	1.00	17.46	A	C
ATOM	66	CD2	LEU	A	6	71.748	54.997	-5.797	1.00	21.42	A	C
ATOM	67	N	ARG	A	7	76.173	53.126	-6.364	1.00	21.10	A	N
ATOM	68	CA	ARG	A	7	77.333	52.266	-6.230	1.00	23.84	A	C
ATOM	69	C	ARG	A	7	77.237	51.485	-4.939	1.00	25.78	A	C
ATOM	70	O	ARG	A	7	76.424	51.808	-4.059	1.00	21.54	A	O
ATOM	71	CB	ARG	A	7	78.610	53.103	-6.226	1.00	26.25	A	C
ATOM	72	CG	ARG	A	7	78.992	53.658	-7.583	1.00	30.55	A	C
ATOM	73	CD	ARG	A	7	80.135	54.652	-7.549	1.00	37.65	A	C
ATOM	74	NE	ARG	A	7	80.063	55.407	-8.932	0.00	40.50	A	N

ATOM	75	CZ	ARG	A	7	80.997	56.306	-9.222	0.00	41.92	A	C
ATOM	76	NH1	ARG	A	7	80.991	56.911	-10.402	0.00	42.93	A	N
ATOM	77	NH2	ARG	A	7	81.937	56.601	-8.335	0.00	42.80	A	N
ATOM	78	N	GLY	A	8	78.091	50.479	-4.799	1.00	26.16	A	N
ATOM	79	CA	GLY	A	8	78.086	49.663	-3.598	1.00	29.54	A	C
ATOM	80	C	GLY	A	8	79.032	48.490	-3.639	1.00	31.18	A	C
ATOM	81	O	GLY	A	8	79.790	48.325	-4.591	1.00	33.68	A	O
ATOM	82	N	LYS	A	9	78.986	47.685	-2.587	1.00	34.88	A	N
ATOM	83	CA	LYS	A	9	79.643	46.390	-2.578	1.00	36.27	A	C
ATOM	84	C	LYS	A	9	78.625	45.337	-2.169	1.00	37.50	A	C
ATOM	85	O	LYS	A	9	77.771	45.576	-1.316	1.00	32.87	A	O
ATOM	86	CB	LYS	A	9	80.861	46.396	-1.649	1.00	39.66	A	C
ATOM	87	CG	LYS	A	9	81.975	47.324	-2.120	1.00	45.29	A	C
ATOM	88	CD	LYS	A	9	83.346	46.635	-2.207	1.00	50.21	A	C
ATOM	89	CE	LYS	A	9	84.382	47.543	-2.887	1.00	52.01	A	C
ATOM	90	NZ	LYS	A	9	85.408	48.085	-1.943	1.00	53.23	A	N
ATOM	91	N	SER	A	10	78.708	44.172	-2.805	1.00	38.65	A	N
ATOM	92	CA	SER	A	10	77.807	43.063	-2.525	1.00	39.77	A	C
ATOM	93	C	SER	A	10	77.658	42.852	-1.026	1.00	38.92	A	C
ATOM	94	O	SER	A	10	78.658	42.718	-0.316	1.00	38.89	A	O
ATOM	95	CB	SER	A	10	78.336	41.776	-3.172	1.00	41.88	A	C
ATOM	96	OG	SER	A	10	77.485	40.680	-2.879	1.00	44.59	A	O
ATOM	97	N	GLY	A	11	76.410	42.857	-0.556	1.00	36.41	A	N
ATOM	98	CA	GLY	A	11	76.097	42.627	0.843	1.00	35.71	A	C
ATOM	99	C	GLY	A	11	76.076	43.859	1.738	1.00	35.38	A	C
ATOM	100	O	GLY	A	11	75.631	43.757	2.886	1.00	37.81	A	O
ATOM	101	N	GLN	A	12	76.519	45.005	1.213	1.00	34.18	A	N
ATOM	102	CA	GLN	A	12	76.732	46.234	1.999	1.00	35.64	A	C
ATOM	103	C	GLN	A	12	75.861	47.409	1.536	1.00	35.07	A	C
ATOM	104	O	GLN	A	12	76.148	48.558	1.881	1.00	36.40	A	O
ATOM	105	CB	GLN	A	12	78.196	46.693	1.913	1.00	37.52	A	C
ATOM	106	CG	GLN	A	12	79.230	45.703	2.437	1.00	42.55	A	C
ATOM	107	CD	GLN	A	12	80.653	46.267	2.465	1.00	40.98	A	C
ATOM	108	OE1	GLN	A	12	81.562	45.623	2.984	1.00	49.77	A	O
ATOM	109	NE2	GLN	A	12	80.846	47.450	1.904	1.00	50.11	A	N
ATOM	110	N	GLY	A	13	74.824	47.132	0.749	1.00	30.97	A	N
ATOM	111	CA	GLY	A	13	73.887	48.163	0.331	1.00	27.55	A	C
ATOM	112	C	GLY	A	13	74.366	49.021	-0.820	1.00	25.65	A	C
ATOM	113	O	GLY	A	13	75.491	48.904	-1.289	1.00	26.10	A	O
ATOM	114	N	TYR	A	14	73.477	49.892	-1.275	1.00	17.01	A	N
ATOM	115	CA	TYR	A	14	73.738	50.794	-2.395	1.00	17.38	A	C
ATOM	116	C	TYR	A	14	73.722	52.218	-1.880	1.00	16.80	A	C
ATOM	117	O	TYR	A	14	72.851	52.561	-1.072	1.00	17.47	A	O
ATOM	118	CB	TYR	A	14	72.635	50.663	-3.446	1.00	18.29	A	C
ATOM	119	CG	TYR	A	14	72.651	49.339	-4.162	1.00	21.45	A	C
ATOM	120	CD1	TYR	A	14	72.134	48.194	-3.574	1.00	20.72	A	C
ATOM	121	CD2	TYR	A	14	73.201	49.239	-5.434	1.00	21.04	A	C
ATOM	122	CE1	TYR	A	14	72.164	46.981	-4.246	1.00	20.87	A	C
ATOM	123	CE2	TYR	A	14	73.233	48.043	-6.101	1.00	23.36	A	C
ATOM	124	CZ	TYR	A	14	72.723	46.935	-5.522	1.00	24.50	A	C
ATOM	125	OH	TYR	A	14	72.758	45.757	-6.229	1.00	27.32	A	O
ATOM	126	N	TYR	A	15	74.636	53.044	-2.387	1.00	18.15	A	N
ATOM	127	CA	TYR	A	15	74.727	54.431	-1.976	1.00	15.54	A	C
ATOM	128	C	TYR	A	15	74.734	55.415	-3.133	1.00	16.89	A	C
ATOM	129	O	TYR	A	15	75.171	55.108	-4.243	1.00	17.87	A	O
ATOM	130	CB	TYR	A	15	75.951	54.666	-1.064	1.00	16.46	A	C
ATOM	131	CG	TYR	A	15	77.308	54.342	-1.685	1.00	15.58	A	C
ATOM	132	CD1	TYR	A	15	77.966	55.246	-2.501	1.00	19.48	A	C
ATOM	133	CD2	TYR	A	15	77.919	53.139	-1.411	1.00	19.60	A	C
ATOM	134	CE1	TYR	A	15	79.201	54.956	-3.034	1.00	21.95	A	C
ATOM	135	CE2	TYR	A	15	79.165	52.838	-1.926	1.00	23.26	A	C
ATOM	136	CZ	TYR	A	15	79.787	53.734	-2.739	1.00	21.80	A	C
ATOM	137	OH	TYR	A	15	81.006	53.396	-3.255	1.00	26.17	A	O
ATOM	138	N	VAL	A	16	74.279	56.620	-2.823	1.00	17.50	A	N
ATOM	139	CA	VAL	A	16	74.197	57.728	-3.760	1.00	19.34	A	C
ATOM	140	C	VAL	A	16	75.077	58.862	-3.212	1.00	20.35	A	C
ATOM	141	O	VAL	A	16	75.165	59.056	-1.995	1.00	20.27	A	O
ATOM	142	CB	VAL	A	16	72.715	58.201	-3.936	1.00	18.58	A	C
ATOM	143	CG1	VAL	A	16	72.177	58.911	-2.680	1.00	18.67	A	C
ATOM	144	CG2	VAL	A	16	72.554	59.101	-5.172	1.00	21.03	A	C
ATOM	145	N	GLU	A	17	75.715	59.608	-4.101	1.00	20.07	A	N
ATOM	146	CA	GLU	A	17	76.401	60.838	-3.706	1.00	22.44	A	C
ATOM	147	C	GLU	A	17	75.398	61.943	-3.372	1.00	22.83	A	C
ATOM	148	O	GLU	A	17	74.419	62.145	-4.091	1.00	20.94	A	O
ATOM	149	CB	GLU	A	17	77.360	61.298	-4.810	1.00	23.72	A	C
ATOM	150	CG	GLU	A	17	78.246	62.482	-4.416	1.00	28.53	A	C
ATOM	151	CD	GLU	A	17	79.065	63.024	-5.580	1.00	36.53	A	C

ATOM	152	OE1	GLU	A	17	78.956	64.228	-5.878	1.00	39.02	A	O
ATOM	153	OE2	GLU	A	17	79.820	62.249	-6.201	1.00	41.99	A	O
ATOM	154	N	MET	A	18	75.616	62.632	-2.249	1.00	18.64	A	N
ATOM	155	CA	MET	A	18	74.824	63.788	-1.849	1.00	18.78	A	C
ATOM	156	C	MET	A	18	75.744	64.904	-1.365	1.00	24.24	A	C
ATOM	157	O	MET	A	18	76.919	64.671	-1.079	1.00	23.12	A	O
ATOM	158	CB	MET	A	18	73.866	63.427	-0.717	1.00	20.09	A	C
ATOM	159	CG	MET	A	18	72.884	62.284	-1.064	1.00	17.91	A	C
ATOM	160	SD	MET	A	18	71.685	61.911	0.240	1.00	20.92	A	S
ATOM	161	CE	MET	A	18	70.491	63.197	-0.005	1.00	21.35	A	C
ATOM	162	N	THR	A	19	75.229	66.121	-1.313	1.00	24.86	A	N
ATOM	163	CA	THR	A	19	75.966	67.206	-0.661	1.00	26.57	A	C
ATOM	164	C	THR	A	19	75.122	67.794	0.443	1.00	24.45	A	C
ATOM	165	O	THR	A	19	73.904	67.861	0.341	1.00	23.60	A	O
ATOM	166	CB	THR	A	19	76.392	68.292	-1.665	1.00	28.59	A	C
ATOM	167	OG1	THR	A	19	75.236	68.833	-2.311	1.00	32.78	A	O
ATOM	168	CG2	THR	A	19	77.235	67.712	-2.775	1.00	28.11	A	C
ATOM	169	N	VAL	A	20	75.775	68.213	1.531	1.00	25.61	A	N
ATOM	170	CA	VAL	A	20	75.078	68.836	2.643	1.00	22.00	A	C
ATOM	171	C	VAL	A	20	75.826	70.130	2.995	1.00	21.90	A	C
ATOM	172	O	VAL	A	20	77.040	70.183	2.841	1.00	23.44	A	O
ATOM	173	CB	VAL	A	20	75.011	67.902	3.848	1.00	25.28	A	C
ATOM	174	CG1	VAL	A	20	74.361	68.579	5.033	1.00	30.83	A	C
ATOM	175	CG2	VAL	A	20	74.245	66.611	3.495	1.00	25.14	A	C
ATOM	176	N	GLY	A	21	75.077	71.146	3.422	1.00	25.14	A	N
ATOM	177	CA	GLY	A	21	75.623	72.434	3.837	1.00	27.79	A	C
ATOM	178	C	GLY	A	21	76.015	73.417	2.752	1.00	26.88	A	C
ATOM	179	O	GLY	A	21	75.906	73.137	1.551	1.00	27.40	A	O
ATOM	180	N	SER	A	22	76.466	74.594	3.202	1.00	28.28	A	N
ATOM	181	CA	SER	A	22	76.976	75.657	2.330	1.00	29.16	A	C
ATOM	182	C	SER	A	22	78.298	76.173	2.919	1.00	28.62	A	C
ATOM	183	O	SER	A	22	78.308	76.639	4.049	1.00	29.95	A	O
ATOM	184	CB	SER	A	22	75.983	76.815	2.238	1.00	29.69	A	C
ATOM	185	OG	SER	A	22	74.675	76.366	1.925	1.00	29.77	A	O
ATOM	186	N	PRO	A	23	79.407	76.052	2.198	1.00	28.22	A	N
ATOM	187	CA	PRO	A	23	79.461	75.401	0.884	1.00	30.78	A	C
ATOM	188	C	PRO	A	23	79.227	73.886	0.976	1.00	29.87	A	C
ATOM	189	O	PRO	A	23	79.338	73.300	2.063	1.00	25.45	A	O
ATOM	190	CB	PRO	A	23	80.875	75.693	0.407	1.00	31.63	A	C
ATOM	191	CG	PRO	A	23	81.664	75.968	1.651	1.00	29.94	A	C
ATOM	192	CD	PRO	A	23	80.727	76.545	2.629	1.00	33.02	A	C
ATOM	193	N	PRO	A	24	78.894	73.258	-0.145	1.00	30.31	A	N
ATOM	194	CA	PRO	A	24	78.559	71.821	-0.139	1.00	26.63	A	C
ATOM	195	C	PRO	A	24	79.673	70.857	0.304	1.00	25.38	A	C
ATOM	196	O	PRO	A	24	80.807	70.925	-0.155	1.00	25.17	A	O
ATOM	197	CB	PRO	A	24	78.141	71.536	-1.593	1.00	28.22	A	C
ATOM	198	CG	PRO	A	24	78.576	72.715	-2.410	1.00	32.40	A	C
ATOM	199	CD	PRO	A	24	78.778	73.874	-1.484	1.00	33.13	A	C
ATOM	200	N	GLN	A	25	79.292	69.920	1.169	1.00	24.26	A	N
ATOM	201	CA	GLN	A	25	80.144	68.839	1.620	1.00	23.05	A	C
ATOM	202	C	GLN	A	25	79.617	67.576	0.992	1.00	19.90	A	C
ATOM	203	O	GLN	A	25	78.470	67.220	1.220	1.00	20.87	A	O
ATOM	204	CB	GLN	A	25	80.075	68.728	3.127	1.00	20.92	A	C
ATOM	205	CG	GLN	A	25	80.581	69.995	3.817	1.00	25.92	A	C
ATOM	206	CD	GLN	A	25	80.491	69.911	5.317	1.00	24.91	A	C
ATOM	207	OE1	GLN	A	25	80.742	68.850	5.894	1.00	21.17	A	O
ATOM	208	NE2	GLN	A	25	80.153	71.021	5.957	1.00	26.06	A	N
ATOM	209	N	THR	A	26	80.439	66.926	0.187	1.00	23.72	A	N
ATOM	210	CA	THR	A	26	80.041	65.699	-0.495	1.00	23.00	A	C
ATOM	211	C	THR	A	26	80.141	64.498	0.435	1.00	22.59	A	C
ATOM	212	O	THR	A	26	81.151	64.310	1.103	1.00	23.44	A	O
ATOM	213	CB	THR	A	26	80.943	65.456	-1.685	1.00	24.91	A	C
ATOM	214	OG1	THR	A	26	80.891	66.588	-2.566	1.00	31.54	A	O
ATOM	215	CG2	THR	A	26	80.428	64.292	-2.537	1.00	25.28	A	C
ATOM	216	N	LEU	A	27	79.107	63.666	0.430	1.00	19.15	A	N
ATOM	217	CA	LEU	A	27	79.093	62.431	1.198	1.00	18.03	A	C
ATOM	218	C	LEU	A	27	78.394	61.329	0.375	1.00	22.50	A	C
ATOM	219	O	LEU	A	27	77.511	61.636	-0.415	1.00	25.14	A	O
ATOM	220	CB	LEU	A	27	78.310	62.637	2.488	1.00	18.41	A	C
ATOM	221	CG	LEU	A	27	78.805	63.740	3.447	1.00	23.17	A	C
ATOM	222	CD1	LEU	A	27	77.737	64.155	4.429	1.00	28.47	A	C
ATOM	223	CD2	LEU	A	27	80.040	63.300	4.174	1.00	22.35	A	C
ATOM	224	N	ASN	A	28	78.804	60.075	0.562	1.00	19.63	A	N
ATOM	225	CA	ASN	A	28	78.097	58.926	-0.013	1.00	18.44	A	C
ATOM	226	C	ASN	A	28	77.098	58.404	0.985	1.00	17.41	A	C
ATOM	227	O	ASN	A	28	77.467	58.130	2.122	1.00	15.99	A	O
ATOM	228	CB	ASN	A	28	79.059	57.817	-0.346	1.00	17.43	A	C

ATOM	229	CG	ASN	A	28	79.868	58.114	-1.556	1.00	22.09	A	C
ATOM	230	OD1	ASN	A	28	79.407	58.837	-2.434	1.00	21.00	A	O
ATOM	231	ND2	ASN	A	28	81.084	57.573	-1.622	1.00	22.09	A	N
ATOM	232	N	ILE	A	29	75.848	58.222	0.566	1.00	13.33	A	N
ATOM	233	CA	ILE	A	29	74.741	57.964	1.501	1.00	15.06	A	C
ATOM	234	C	ILE	A	29	73.969	56.724	1.072	1.00	15.98	A	C
ATOM	235	O	ILE	A	29	73.495	56.628	-0.071	1.00	16.00	A	O
ATOM	236	CB	ILE	A	29	73.777	59.164	1.569	1.00	17.19	A	C
ATOM	237	CG1	ILE	A	29	74.533	60.443	1.960	1.00	16.84	A	C
ATOM	238	CG2	ILE	A	29	72.625	58.876	2.579	1.00	15.77	A	C
ATOM	239	CD1	ILE	A	29	75.147	60.409	3.359	1.00	18.72	A	C
ATOM	240	N	LEU	A	30	73.829	55.787	1.997	1.00	15.17	A	N
ATOM	241	CA	LEU	A	30	73.110	54.541	1.743	1.00	16.63	A	C
ATOM	242	C	LEU	A	30	71.623	54.825	1.455	1.00	17.89	A	C
ATOM	243	O	LEU	A	30	71.000	55.542	2.186	1.00	17.80	A	O
ATOM	244	CB	LEU	A	30	73.251	53.629	2.964	1.00	14.92	A	C
ATOM	245	CG	LEU	A	30	72.441	52.335	2.947	1.00	24.85	A	C
ATOM	246	CD1	LEU	A	30	73.456	51.336	1.962	0.00	19.90	A	C
ATOM	247	CD2	LEU	A	30	72.418	51.625	4.210	0.00	19.96	A	C
ATOM	248	N	VAL	A	31	71.059	54.224	0.405	1.00	15.67	A	N
ATOM	249	CA	VAL	A	31	69.656	54.390	0.066	1.00	17.96	A	C
ATOM	250	C	VAL	A	31	68.865	53.269	0.715	1.00	18.65	A	C
ATOM	251	O	VAL	A	31	69.101	52.060	0.440	1.00	21.01	A	O
ATOM	252	CB	VAL	A	31	69.461	54.358	-1.471	1.00	21.10	A	C
ATOM	253	CG1	VAL	A	31	67.991	54.309	-1.806	1.00	23.22	A	C
ATOM	254	CG2	VAL	A	31	70.102	55.554	-2.073	1.00	19.69	A	C
ATOM	255	N	ASP	A	32	67.936	53.656	1.591	1.00	18.25	A	N
ATOM	256	CA	ASP	A	32	67.221	52.712	2.456	1.00	20.14	A	C
ATOM	257	C	ASP	A	32	65.712	52.942	2.457	1.00	18.89	A	C
ATOM	258	O	ASP	A	32	65.217	53.839	3.144	1.00	18.73	A	O
ATOM	259	CB	ASP	A	32	67.748	52.832	3.905	1.00	20.81	A	C
ATOM	260	CG	ASP	A	32	67.163	51.747	4.850	1.00	27.29	A	C
ATOM	261	OD1	ASP	A	32	66.652	50.729	4.345	1.00	28.02	A	O
ATOM	262	OD2	ASP	A	32	67.178	51.817	6.113	1.00	29.94	A	O
ATOM	263	N	THR	A	33	64.947	52.108	1.735	1.00	15.71	A	N
ATOM	264	CA	THR	A	33	63.500	52.284	1.753	1.00	16.65	A	C
ATOM	265	C	THR	A	33	62.839	51.643	2.958	1.00	18.62	A	C
ATOM	266	O	THR	A	33	61.627	51.707	3.086	1.00	19.27	A	O
ATOM	267	CB	THR	A	33	62.855	51.726	0.459	1.00	17.78	A	C
ATOM	268	OG1	THR	A	33	63.088	50.330	0.395	1.00	17.76	A	O
ATOM	269	CG2	THR	A	33	63.526	52.289	-0.756	1.00	20.47	A	C
ATOM	270	N	GLY	A	34	63.645	51.078	3.854	1.00	19.46	A	N
ATOM	271	CA	GLY	A	34	63.137	50.457	5.065	1.00	22.82	A	C
ATOM	272	C	GLY	A	34	63.251	51.314	6.315	1.00	24.98	A	C
ATOM	273	O	GLY	A	34	63.033	50.830	7.434	1.00	24.60	A	O
ATOM	274	N	SER	A	35	63.601	52.578	6.130	1.00	18.89	A	N
ATOM	275	CA	SER	A	35	63.672	53.543	7.231	1.00	21.21	A	C
ATOM	276	C	SER	A	35	63.376	54.978	6.749	1.00	18.57	A	C
ATOM	277	O	SER	A	35	63.245	55.229	5.535	1.00	21.32	A	O
ATOM	278	CB	SER	A	35	65.045	53.420	7.880	1.00	21.69	A	C
ATOM	279	OG	SER	A	35	66.063	53.982	7.078	1.00	20.28	A	O
ATOM	280	N	SER	A	36	63.253	55.940	7.678	1.00	18.30	A	N
ATOM	281	CA	SER	A	36	62.727	57.267	7.347	1.00	20.36	A	C
ATOM	282	C	SER	A	36	63.545	58.455	7.889	1.00	21.41	A	C
ATOM	283	O	SER	A	36	63.101	59.594	7.809	1.00	19.92	A	O
ATOM	284	CB	SER	A	36	61.267	57.375	7.824	1.00	25.82	A	C
ATOM	285	OG	SER	A	36	60.485	56.344	7.230	1.00	25.30	A	O
ATOM	286	N	ASN	A	37	64.748	58.181	8.396	1.00	19.59	A	N
ATOM	287	CA	ASN	A	37	65.676	59.222	8.853	1.00	20.44	A	C
ATOM	288	C	ASN	A	37	66.852	59.444	7.907	1.00	17.40	A	C
ATOM	289	O	ASN	A	37	67.426	58.484	7.386	1.00	17.40	A	O
ATOM	290	CB	ASN	A	37	66.262	58.847	10.225	1.00	19.75	A	C
ATOM	291	CG	ASN	A	37	65.330	59.162	11.365	1.00	25.09	A	C
ATOM	292	OD1	ASN	A	37	65.323	60.288	11.888	1.00	26.01	A	O
ATOM	293	ND2	ASN	A	37	64.555	58.177	11.776	1.00	21.61	A	N
ATOM	294	N	PHE	A	38	67.217	60.704	7.697	1.00	18.60	A	N
ATOM	295	CA	PHE	A	38	68.450	61.064	7.013	1.00	17.76	A	C
ATOM	296	C	PHE	A	38	69.494	61.330	8.089	1.00	17.46	A	C
ATOM	297	O	PHE	A	38	69.356	62.288	8.837	1.00	18.26	A	O
ATOM	298	CB	PHE	A	38	68.236	62.307	6.143	1.00	17.46	A	C
ATOM	299	CG	PHE	A	38	69.466	62.776	5.366	1.00	18.60	A	C
ATOM	300	CD1	PHE	A	38	70.391	61.896	4.828	1.00	17.37	A	C
ATOM	301	CD2	PHE	A	38	69.657	64.124	5.127	1.00	24.93	A	C
ATOM	302	CE1	PHE	A	38	71.488	62.350	4.104	1.00	19.65	A	C
ATOM	303	CE2	PHE	A	38	70.747	64.586	4.384	1.00	19.49	A	C
ATOM	304	CZ	PHE	A	38	71.669	63.701	3.881	1.00	23.24	A	C
ATOM	305	N	ALA	A	39	70.467	60.430	8.224	1.00	18.71	A	N

ATOM	306	CA	ALA	A	39	71.480	60.508	9.272	1.00	18.80	A	C
ATOM	307	C	ALA	A	39	72.866	60.348	8.667	1.00	20.90	A	C
ATOM	308	O	ALA	A	39	73.104	59.439	7.862	1.00	20.32	A	O
ATOM	309	CB	ALA	A	39	71.225	59.457	10.334	1.00	17.93	A	C
ATOM	310	N	VAL	A	40	73.792	61.223	9.058	1.00	19.20	A	N
ATOM	311	CA	VAL	A	40	75.145	61.189	8.526	1.00	18.03	A	C
ATOM	312	C	VAL	A	40	76.193	61.242	9.640	1.00	18.42	A	C
ATOM	313	O	VAL	A	40	76.027	61.985	10.580	1.00	15.83	A	O
ATOM	314	CB	VAL	A	40	75.398	62.372	7.587	1.00	19.32	A	C
ATOM	315	CG1	VAL	A	40	74.430	62.354	6.382	1.00	24.72	A	C
ATOM	316	CG2	VAL	A	40	75.304	63.711	8.319	1.00	25.33	A	C
ATOM	317	N	GLY	A	41	77.272	60.490	9.488	1.00	18.41	A	N
ATOM	318	CA	GLY	A	41	78.444	60.626	10.354	1.00	13.03	A	C
ATOM	319	C	GLY	A	41	78.921	62.049	10.463	1.00	16.57	A	C
ATOM	320	O	GLY	A	41	78.986	62.780	9.486	1.00	16.35	A	O
ATOM	321	N	ALA	A	42	79.186	62.482	11.688	1.00	18.46	A	N
ATOM	322	CA	ALA	A	42	79.513	63.880	11.952	1.00	16.09	A	C
ATOM	323	C	ALA	A	42	80.745	63.987	12.843	1.00	21.94	A	C
ATOM	324	O	ALA	A	42	81.068	65.059	13.334	1.00	21.99	A	O
ATOM	325	CB	ALA	A	42	78.326	64.558	12.613	1.00	19.21	A	C
ATOM	326	N	ALA	A	43	81.444	62.873	12.985	1.00	17.43	A	N
ATOM	327	CA	ALA	A	43	82.584	62.752	13.899	1.00	19.03	A	C
ATOM	328	C	ALA	A	43	83.590	61.822	13.222	1.00	22.11	A	C
ATOM	329	O	ALA	A	43	83.186	60.977	12.414	1.00	18.84	A	O
ATOM	330	CB	ALA	A	43	82.131	62.185	15.216	1.00	20.66	A	C
ATOM	331	N	PRO	A	44	84.880	61.964	13.530	1.00	21.75	A	N
ATOM	332	CA	PRO	A	44	85.928	61.128	12.903	1.00	22.99	A	C
ATOM	333	C	PRO	A	44	86.039	59.692	13.422	1.00	21.03	A	C
ATOM	334	O	PRO	A	44	87.044	59.283	13.989	1.00	22.42	A	O
ATOM	335	CB	PRO	A	44	87.204	61.930	13.173	1.00	23.97	A	C
ATOM	336	CG	PRO	A	44	86.923	62.655	14.467	1.00	21.28	A	C
ATOM	337	CD	PRO	A	44	85.466	63.000	14.406	1.00	22.65	A	C
ATOM	338	N	HIS	A	45	85.004	58.904	13.175	1.00	19.15	A	N
ATOM	339	CA	HIS	A	45	85.011	57.491	13.493	1.00	19.87	A	C
ATOM	340	C	HIS	A	45	86.074	56.884	12.559	1.00	23.49	A	C
ATOM	341	O	HIS	A	45	86.161	57.279	11.408	1.00	18.76	A	O
ATOM	342	CB	HIS	A	45	83.600	56.898	13.231	1.00	20.18	A	C
ATOM	343	CG	HIS	A	45	83.499	55.426	13.491	1.00	20.56	A	C
ATOM	344	ND1	HIS	A	45	82.921	54.900	14.628	1.00	27.21	A	N
ATOM	345	CD2	HIS	A	45	83.911	54.369	12.753	1.00	20.97	A	C
ATOM	346	CE1	HIS	A	45	82.989	53.579	14.577	1.00	20.15	A	C
ATOM	347	NE2	HIS	A	45	83.572	53.234	13.443	1.00	26.79	A	N
ATOM	348	N	PRO	A	46	86.900	55.958	13.039	1.00	23.59	A	N
ATOM	349	CA	PRO	A	46	87.999	55.418	12.221	1.00	26.27	A	C
ATOM	350	C	PRO	A	46	87.618	54.722	10.881	1.00	23.39	A	C
ATOM	351	O	PRO	A	46	88.449	54.679	9.975	1.00	27.08	A	O
ATOM	352	CB	PRO	A	46	88.677	54.416	13.175	1.00	24.42	A	C
ATOM	353	CG	PRO	A	46	87.621	54.034	14.147	1.00	27.39	A	C
ATOM	354	CD	PRO	A	46	86.863	55.335	14.378	1.00	25.05	A	C
ATOM	355	N	PHE	A	47	86.410	54.192	10.783	1.00	25.26	A	N
ATOM	356	CA	PHE	A	47	85.924	53.538	9.560	1.00	25.03	A	C
ATOM	357	C	PHE	A	47	85.523	54.517	8.446	1.00	22.84	A	C
ATOM	358	O	PHE	A	47	85.309	54.084	7.325	1.00	25.36	A	O
ATOM	359	CB	PHE	A	47	84.678	52.671	9.832	1.00	27.84	A	C
ATOM	360	CG	PHE	A	47	84.888	51.503	10.769	1.00	32.30	A	C
ATOM	361	CD1	PHE	A	47	86.141	51.176	11.282	1.00	36.05	A	C
ATOM	362	CD2	PHE	A	47	83.794	50.722	11.134	1.00	35.59	A	C
ATOM	363	CE1	PHE	A	47	86.297	50.098	12.133	1.00	32.80	A	C
ATOM	364	CE2	PHE	A	47	83.945	49.635	12.004	1.00	36.20	A	C
ATOM	365	CZ	PHE	A	47	85.197	49.326	12.489	1.00	37.31	A	C
ATOM	366	N	LEU	A	48	85.377	55.804	8.761	1.00	19.13	A	N
ATOM	367	CA	LEU	A	48	84.818	56.789	7.835	1.00	18.71	A	C
ATOM	368	C	LEU	A	48	85.829	57.499	6.963	1.00	22.04	A	C
ATOM	369	O	LEU	A	48	86.798	58.086	7.451	1.00	22.43	A	O
ATOM	370	CB	LEU	A	48	84.019	57.848	8.602	1.00	17.69	A	C
ATOM	371	CG	LEU	A	48	82.797	57.361	9.367	1.00	14.97	A	C
ATOM	372	CD1	LEU	A	48	82.068	58.567	9.926	1.00	18.29	A	C
ATOM	373	CD2	LEU	A	48	81.839	56.567	8.517	1.00	19.80	A	C
ATOM	374	N	HIS	A	49	85.553	57.517	5.666	1.00	19.90	A	N
ATOM	375	CA	HIS	A	49	86.310	58.348	4.715	1.00	23.16	A	C
ATOM	376	C	HIS	A	49	86.115	59.862	4.903	1.00	23.74	A	C
ATOM	377	O	HIS	A	49	87.033	60.658	4.676	1.00	24.96	A	O
ATOM	378	CB	HIS	A	49	85.901	58.027	3.277	1.00	24.78	A	C
ATOM	379	CG	HIS	A	49	86.253	56.648	2.822	1.00	18.81	A	C
ATOM	380	ND1	HIS	A	49	87.368	56.386	2.054	1.00	23.64	A	N
ATOM	381	CD2	HIS	A	49	85.623	55.463	2.989	1.00	17.53	A	C
ATOM	382	CE1	HIS	A	49	87.408	55.095	1.779	1.00	20.49	A	C

ATOM	383	NE2	HIS	A	49	86.361	54.512	2.331	1.00	25.00	A	N
ATOM	384	N	ARG	A	50	84.900	60.274	5.255	1.00	23.13	A	N
ATOM	385	CA	ARG	A	50	84.603	61.682	5.496	1.00	24.92	A	C
ATOM	386	C	ARG	A	50	83.387	61.768	6.398	1.00	22.50	A	C
ATOM	387	O	ARG	A	50	82.761	60.763	6.692	1.00	20.11	A	O
ATOM	388	CB	ARG	A	50	84.335	62.435	4.200	1.00	31.00	A	C
ATOM	389	CG	ARG	A	50	84.028	61.549	3.065	1.00	30.52	A	C
ATOM	390	CD	ARG	A	50	83.871	62.231	1.758	1.00	33.45	A	C
ATOM	391	NE	ARG	A	50	83.103	61.374	0.862	1.00	35.30	A	N
ATOM	392	CZ	ARG	A	50	82.912	61.613	-0.430	1.00	41.98	A	C
ATOM	393	NH1	ARG	A	50	83.440	62.692	-1.000	1.00	41.62	A	N
ATOM	394	NH2	ARG	A	50	82.188	60.765	-1.159	1.00	41.63	A	N
ATOM	395	N	TYR	A	51	83.097	62.978	6.868	1.00	19.69	A	N
ATOM	396	CA	TYR	A	51	81.968	63.193	7.727	1.00	19.01	A	C
ATOM	397	C	TYR	A	51	81.513	64.641	7.644	1.00	17.45	A	C
ATOM	398	O	TYR	A	51	82.257	65.509	7.198	1.00	19.82	A	O
ATOM	399	CB	TYR	A	51	82.305	62.792	9.175	1.00	17.00	A	C
ATOM	400	CG	TYR	A	51	83.594	63.414	9.694	1.00	19.81	A	C
ATOM	401	CD1	TYR	A	51	84.807	62.799	9.494	1.00	22.49	A	C
ATOM	402	CD2	TYR	A	51	83.574	64.625	10.391	1.00	27.51	A	C
ATOM	403	CE1	TYR	A	51	85.996	63.363	9.962	1.00	29.01	A	C
ATOM	404	CE2	TYR	A	51	84.755	65.198	10.853	1.00	22.34	A	C
ATOM	405	CZ	TYR	A	51	85.959	64.561	10.639	1.00	26.38	A	C
ATOM	406	OH	TYR	A	51	87.153	65.103	11.102	1.00	27.75	A	O
ATOM	407	N	TYR	A	52	80.267	64.861	8.039	1.00	16.76	A	N
ATOM	408	CA	TYR	A	52	79.630	66.167	8.044	1.00	15.41	A	C
ATOM	409	C	TYR	A	52	80.251	67.057	9.094	1.00	18.19	A	C
ATOM	410	O	TYR	A	52	80.252	66.703	10.268	1.00	18.86	A	O
ATOM	411	CB	TYR	A	52	78.163	65.968	8.360	1.00	16.96	A	C
ATOM	412	CG	TYR	A	52	77.241	67.158	8.365	1.00	17.78	A	C
ATOM	413	CD1	TYR	A	52	77.491	68.311	7.617	1.00	19.54	A	C
ATOM	414	CD2	TYR	A	52	76.057	67.095	9.075	1.00	20.48	A	C
ATOM	415	CE1	TYR	A	52	76.608	69.378	7.664	1.00	17.41	A	C
ATOM	416	CE2	TYR	A	52	75.160	68.137	9.089	1.00	21.75	A	C
ATOM	417	CZ	TYR	A	52	75.443	69.280	8.373	1.00	20.07	A	C
ATOM	418	OH	TYR	A	52	74.507	70.291	8.424	1.00	24.27	A	O
ATOM	419	N	GLN	A	53	80.748	68.214	8.671	1.00	21.06	A	N
ATOM	420	CA	GLN	A	53	81.372	69.186	9.580	1.00	22.83	A	C
ATOM	421	C	GLN	A	53	80.474	70.420	9.662	1.00	18.33	A	C
ATOM	422	O	GLN	A	53	80.601	71.340	8.878	1.00	23.76	A	O
ATOM	423	CB	GLN	A	53	82.779	69.535	9.079	1.00	22.30	A	C
ATOM	424	CG	GLN	A	53	83.750	68.353	9.108	1.00	24.84	A	C
ATOM	425	CD	GLN	A	53	85.187	68.690	8.695	1.00	31.20	A	C
ATOM	426	OE1	GLN	A	53	85.490	68.915	7.504	1.00	32.31	A	O
ATOM	427	NE2	GLN	A	53	86.080	68.696	9.671	1.00	27.07	A	N
ATOM	428	N	ARG	A	54	79.537	70.385	10.597	1.00	20.86	A	N
ATOM	429	CA	ARG	A	54	78.545	71.442	10.758	1.00	21.52	A	C
ATOM	430	C	ARG	A	54	79.164	72.827	10.939	1.00	25.15	A	C
ATOM	431	O	ARG	A	54	78.568	73.828	10.536	1.00	26.20	A	O
ATOM	432	CB	ARG	A	54	77.629	71.138	11.918	1.00	21.46	A	C
ATOM	433	CG	ARG	A	54	76.652	69.995	11.655	1.00	22.36	A	C
ATOM	434	CD	ARG	A	54	75.989	69.437	12.869	1.00	24.51	A	C
ATOM	435	NE	ARG	A	54	76.919	68.779	13.780	1.00	20.24	A	N
ATOM	436	CZ	ARG	A	54	76.609	68.376	14.997	1.00	23.34	A	C
ATOM	437	NH1	ARG	A	54	75.389	68.574	15.485	1.00	26.99	A	N
ATOM	438	NH2	ARG	A	54	77.534	67.786	15.739	1.00	21.22	A	N
ATOM	439	N	GLN	A	55	80.362	72.880	11.523	1.00	25.18	A	N
ATOM	440	CA	GLN	A	55	81.055	74.153	11.741	1.00	25.49	A	C
ATOM	441	C	GLN	A	55	81.403	74.886	10.453	1.00	27.22	A	C
ATOM	442	O	GLN	A	55	81.623	76.106	10.471	1.00	31.96	A	O
ATOM	443	CB	GLN	A	55	82.342	73.951	12.586	1.00	25.44	A	C
ATOM	444	CG	GLN	A	55	83.508	73.285	11.866	1.00	26.87	A	C
ATOM	445	CD	GLN	A	55	83.607	71.787	12.100	1.00	22.47	A	C
ATOM	446	OE1	GLN	A	55	84.649	71.186	11.858	1.00	28.14	A	O
ATOM	447	NE2	GLN	A	55	82.531	71.192	12.526	1.00	19.06	A	N
ATOM	448	N	LEU	A	56	81.478	74.148	9.347	1.00	26.29	A	N
ATOM	449	CA	LEU	A	56	81.846	74.711	8.055	1.00	26.09	A	C
ATOM	450	C	LEU	A	56	80.646	75.193	7.224	1.00	28.01	A	C
ATOM	451	O	LEU	A	56	80.835	75.716	6.131	1.00	30.64	A	O
ATOM	452	CB	LEU	A	56	82.667	73.703	7.251	1.00	28.42	A	C
ATOM	453	CG	LEU	A	56	83.966	73.147	7.849	1.00	29.81	A	C
ATOM	454	CD1	LEU	A	56	84.685	72.309	6.814	1.00	33.56	A	C
ATOM	455	CD2	LEU	A	56	84.896	74.243	8.364	1.00	28.02	A	C
ATOM	456	N	SER	A	57	79.432	75.055	7.760	1.00	27.95	A	N
ATOM	457	CA	SER	A	57	78.199	75.322	7.009	1.00	27.26	A	C
ATOM	458	C	SER	A	57	77.432	76.528	7.548	1.00	26.45	A	C
ATOM	459	O	SER	A	57	76.970	76.523	8.701	1.00	27.40	A	O

ATOM	460	CB	SER	A	57	77.287	74.086	7.037	1.00	27.30	A	C
ATOM	461	OG	SER	A	57	76.004	74.353	6.482	1.00	24.82	A	O
ATOM	462	N	SER	A	58	77.250	77.541	6.704	1.00	31.30	A	N
ATOM	463	CA	SER	A	58	76.540	78.753	7.112	1.00	33.18	A	C
ATOM	464	C	SER	A	58	75.049	78.502	7.294	1.00	33.96	A	C
ATOM	465	O	SER	A	58	74.367	79.198	8.059	1.00	31.39	A	O
ATOM	466	CB	SER	A	58	76.761	79.879	6.097	1.00	35.14	A	C
ATOM	467	OG	SER	A	58	76.449	79.481	4.769	1.00	35.98	A	O
ATOM	468	N	THR	A	59	74.552	77.473	6.608	1.00	31.44	A	N
ATOM	469	CA	THR	A	59	73.128	77.222	6.528	1.00	28.82	A	C
ATOM	470	C	THR	A	59	72.637	76.209	7.545	1.00	27.75	A	C
ATOM	471	O	THR	A	59	71.431	75.989	7.648	1.00	26.38	A	O
ATOM	472	CB	THR	A	59	72.745	76.825	5.079	1.00	30.74	A	C
ATOM	473	OG1	THR	A	59	73.712	75.937	4.512	1.00	26.79	A	O
ATOM	474	CG2	THR	A	59	72.851	78.040	4.175	1.00	31.50	A	C
ATOM	475	N	TYR	A	60	73.559	75.630	8.325	1.00	25.76	A	N
ATOM	476	CA	TYR	A	60	73.204	74.716	9.405	1.00	27.01	A	C
ATOM	477	C	TYR	A	60	72.359	75.391	10.487	1.00	30.17	A	C
ATOM	478	O	TYR	A	60	72.671	76.504	10.908	1.00	32.85	A	O
ATOM	479	CB	TYR	A	60	74.475	74.108	10.024	1.00	29.24	A	C
ATOM	480	CG	TYR	A	60	74.208	73.401	11.319	1.00	32.58	A	C
ATOM	481	CD1	TYR	A	60	73.616	72.137	11.341	1.00	33.45	A	C
ATOM	482	CD2	TYR	A	60	74.507	74.016	12.539	1.00	35.22	A	C
ATOM	483	CE1	TYR	A	60	73.344	71.495	12.545	1.00	34.91	A	C
ATOM	484	CE2	TYR	A	60	74.242	73.384	13.741	1.00	35.99	A	C
ATOM	485	CZ	TYR	A	60	73.661	72.128	13.739	1.00	36.24	A	C
ATOM	486	OH	TYR	A	60	73.406	71.510	14.936	1.00	40.70	A	O
ATOM	487	N	ARG	A	61	71.302	74.710	10.934	1.00	29.78	A	N
ATOM	488	CA	ARG	A	61	70.489	75.137	12.074	1.00	32.29	A	C
ATOM	489	C	ARG	A	61	70.289	73.992	13.056	1.00	35.05	A	C
ATOM	490	O	ARG	A	61	69.781	72.931	12.695	1.00	33.45	A	O
ATOM	491	CB	ARG	A	61	69.113	75.638	11.635	1.00	34.98	A	C
ATOM	492	CG	ARG	A	61	69.146	76.790	10.663	1.00	33.55	A	C
ATOM	493	CD	ARG	A	61	67.756	77.209	10.187	1.00	39.45	A	C
ATOM	494	NE	ARG	A	61	67.802	78.053	8.991	1.00	43.50	A	N
ATOM	495	CZ	ARG	A	61	66.737	78.400	8.267	1.00	43.32	A	C
ATOM	496	NH1	ARG	A	61	65.517	77.969	8.591	1.00	43.64	A	N
ATOM	497	NH2	ARG	A	61	66.896	79.173	7.201	1.00	43.55	A	N
ATOM	498	N	ASP	A	62	70.681	74.222	14.302	1.00	32.81	A	N
ATOM	499	CA	ASP	A	62	70.488	73.277	15.385	1.00	34.32	A	C
ATOM	500	C	ASP	A	62	69.019	73.222	15.812	1.00	35.83	A	C
ATOM	501	O	ASP	A	62	68.368	74.257	15.972	1.00	37.43	A	O
ATOM	502	CB	ASP	A	62	71.385	73.703	16.561	1.00	36.21	A	C
ATOM	503	CG	ASP	A	62	71.724	72.567	17.509	1.00	37.73	A	C
ATOM	504	OD1	ASP	A	62	71.078	71.513	17.462	1.00	39.38	A	O
ATOM	505	OD2	ASP	A	62	72.632	72.654	18.366	1.00	38.06	A	O
ATOM	506	N	LEU	A	63	68.504	72.009	16.000	1.00	32.04	A	N
ATOM	507	CA	LEU	A	63	67.151	71.799	16.496	1.00	33.21	A	C
ATOM	508	C	LEU	A	63	67.155	71.580	18.003	1.00	31.37	A	C
ATOM	509	O	LEU	A	63	66.108	71.522	18.621	1.00	33.62	A	O
ATOM	510	CB	LEU	A	63	66.489	70.603	15.793	1.00	32.30	A	C
ATOM	511	CG	LEU	A	63	65.919	70.957	14.417	1.00	37.47	A	C
ATOM	512	CD1	LEU	A	63	65.566	69.688	13.604	1.00	37.52	A	C
ATOM	513	CD2	LEU	A	63	64.696	71.880	14.549	1.00	37.36	A	C
ATOM	514	N	ARG	A	64	68.345	71.460	18.580	1.00	34.84	A	N
ATOM	515	CA	ARG	A	64	68.514	71.279	20.012	1.00	34.85	A	C
ATOM	516	C	ARG	A	64	67.687	70.109	20.516	1.00	37.89	A	C
ATOM	517	O	ARG	A	64	66.925	70.220	21.474	1.00	37.04	A	O
ATOM	518	CB	ARG	A	64	68.180	72.583	20.753	1.00	37.97	A	C
ATOM	519	CG	ARG	A	64	68.865	73.821	20.152	1.00	37.97	A	C
ATOM	520	CD	ARG	A	64	68.726	75.089	21.000	1.00	41.38	A	C
ATOM	521	NE	ARG	A	64	69.447	74.699	22.367	0.00	47.96	A	N
ATOM	522	CZ	ARG	A	64	69.722	75.629	23.275	0.00	49.03	A	C
ATOM	523	NH1	ARG	A	64	69.491	76.907	23.009	0.00	49.64	A	N
ATOM	524	NH2	ARG	A	64	70.226	75.281	24.451	0.00	49.89	A	N
ATOM	525	N	LYS	A	65	67.844	68.973	19.843	1.00	34.71	A	N
ATOM	526	CA	LYS	A	65	67.212	67.732	20.266	1.00	35.06	A	C
ATOM	527	C	LYS	A	65	68.076	66.577	19.771	1.00	30.42	A	C
ATOM	528	O	LYS	A	65	68.655	66.665	18.695	1.00	31.69	A	O
ATOM	529	CB	LYS	A	65	65.801	67.642	19.676	1.00	39.80	A	C
ATOM	530	CG	LYS	A	65	64.967	66.448	20.138	1.00	43.42	A	C
ATOM	531	CD	LYS	A	65	63.513	66.564	19.672	1.00	47.97	A	C
ATOM	532	CE	LYS	A	65	62.653	65.440	20.263	1.00	50.01	A	C
ATOM	533	NZ	LYS	A	65	61.233	65.463	19.797	1.00	51.34	A	N
ATOM	534	N	GLY	A	66	68.190	65.522	20.565	1.00	31.22	A	N
ATOM	535	CA	GLY	A	66	68.910	64.339	20.149	1.00	31.55	A	C
ATOM	536	C	GLY	A	66	67.996	63.249	19.616	1.00	32.06	A	C

ATOM	537	O	GLY	A	66	66.772	63.399	19.632	1.00	33.71	A	O
ATOM	538	N	VAL	A	67	68.617	62.153	19.163	1.00	30.61	A	N
ATOM	539	CA	VAL	A	67	67.927	60.946	18.675	1.00	32.04	A	C
ATOM	540	C	VAL	A	67	68.756	59.693	18.978	1.00	32.39	A	C
ATOM	541	O	VAL	A	67	69.982	59.724	18.870	1.00	29.49	A	O
ATOM	542	CB	VAL	A	67	67.663	61.024	17.158	1.00	34.97	A	C
ATOM	543	CG1	VAL	A	67	66.568	61.988	16.878	1.00	40.45	A	C
ATOM	544	CG2	VAL	A	67	68.912	61.440	16.387	1.00	36.19	A	C
ATOM	545	N	TYR	A	68	68.108	58.602	19.384	1.00	32.50	A	N
ATOM	546	CA	TYR	A	68	68.817	57.361	19.709	1.00	36.46	A	C
ATOM	547	C	TYR	A	68	68.113	56.190	19.062	1.00	34.88	A	C
ATOM	548	O	TYR	A	68	66.962	55.916	19.383	1.00	36.97	A	O
ATOM	549	CB	TYR	A	68	68.902	57.148	21.229	1.00	36.07	A	C
ATOM	550	CG	TYR	A	68	69.801	55.993	21.670	1.00	41.81	A	C
ATOM	551	CD1	TYR	A	68	69.460	54.665	21.395	1.00	43.38	A	C
ATOM	552	CD2	TYR	A	68	70.981	56.226	22.379	1.00	44.20	A	C
ATOM	553	CE1	TYR	A	68	70.274	53.605	21.798	1.00	43.39	A	C
ATOM	554	CE2	TYR	A	68	71.805	55.167	22.789	1.00	44.55	A	C
ATOM	555	CZ	TYR	A	68	71.444	53.863	22.492	1.00	45.41	A	C
ATOM	556	OH	TYR	A	68	72.242	52.807	22.897	1.00	47.48	A	O
ATOM	557	N	VAL	A	69	68.826	55.477	18.196	1.00	33.48	A	N
ATOM	558	CA	VAL	A	69	68.249	54.404	17.376	1.00	34.57	A	C
ATOM	559	C	VAL	A	69	68.922	53.080	17.716	1.00	34.34	A	C
ATOM	560	O	VAL	A	69	69.996	52.793	17.192	1.00	28.53	A	O
ATOM	561	CB	VAL	A	69	68.440	54.691	15.866	1.00	35.13	A	C
ATOM	562	CG1	VAL	A	69	67.944	53.526	15.002	1.00	38.45	A	C
ATOM	563	CG2	VAL	A	69	67.754	56.000	15.484	1.00	36.74	A	C
ATOM	564	N	PRO	A	70	68.319	52.269	18.588	1.00	39.88	A	N
ATOM	565	CA	PRO	A	70	68.846	50.922	18.830	1.00	43.50	A	C
ATOM	566	C	PRO	A	70	68.577	50.028	17.629	1.00	47.11	A	C
ATOM	567	O	PRO	A	70	67.551	50.175	16.960	1.00	41.77	A	O
ATOM	568	CB	PRO	A	70	68.097	50.428	20.077	1.00	44.42	A	C
ATOM	569	CG	PRO	A	70	67.031	51.423	20.368	1.00	43.58	A	C
ATOM	570	CD	PRO	A	70	67.125	52.554	19.397	1.00	42.11	A	C
ATOM	571	N	TYR	A	71	69.527	49.140	17.367	1.00	51.98	A	N
ATOM	572	CA	TYR	A	71	69.474	48.179	16.276	1.00	56.73	A	C
ATOM	573	C	TYR	A	71	69.683	46.796	16.908	1.00	58.39	A	C
ATOM	574	O	TYR	A	71	69.428	46.618	18.105	1.00	57.75	A	O
ATOM	575	CB	TYR	A	71	70.558	48.519	15.229	1.00	57.66	A	C
ATOM	576	CG	TYR	A	71	70.091	49.405	14.090	1.00	59.91	A	C
ATOM	577	CD1	TYR	A	71	70.760	50.591	13.779	1.00	60.36	A	C
ATOM	578	CD2	TYR	A	71	68.995	49.049	13.304	1.00	61.59	A	C
ATOM	579	CE1	TYR	A	71	70.334	51.408	12.725	1.00	60.84	A	C
ATOM	580	CE2	TYR	A	71	68.568	49.857	12.249	1.00	62.07	A	C
ATOM	581	CZ	TYR	A	71	69.241	51.035	11.966	1.00	63.27	A	C
ATOM	582	OH	TYR	A	71	68.818	51.840	10.924	1.00	64.04	A	O
ATOM	583	N	THR	A	72	70.147	45.832	16.114	1.00	61.01	A	N
ATOM	584	CA	THR	A	72	70.319	44.444	16.556	1.00	60.90	A	C
ATOM	585	C	THR	A	72	71.093	44.294	17.877	1.00	59.74	A	C
ATOM	586	O	THR	A	72	70.491	44.060	18.931	1.00	58.04	A	O
ATOM	587	CB	THR	A	72	70.993	43.609	15.431	1.00	62.06	A	C
ATOM	588	OG1	THR	A	72	72.170	44.276	14.951	1.00	61.28	A	O
ATOM	589	CG2	THR	A	72	70.090	43.514	14.196	1.00	63.15	A	C
ATOM	590	N	GLN	A	73	72.418	44.402	17.800	1.00	57.85	A	N
ATOM	591	CA	GLN	A	73	73.287	44.461	18.971	1.00	57.41	A	C
ATOM	592	C	GLN	A	73	74.155	45.726	18.850	1.00	54.83	A	C
ATOM	593	O	GLN	A	73	75.303	45.747	19.299	1.00	57.07	A	O
ATOM	594	CB	GLN	A	73	74.153	43.194	19.060	1.00	58.83	A	C
ATOM	595	CG	GLN	A	73	73.865	42.294	20.273	1.00	60.65	A	C
ATOM	596	CD	GLN	A	73	74.720	42.630	21.504	1.00	63.27	A	C
ATOM	597	OE1	GLN	A	73	75.959	42.582	21.450	1.00	61.11	A	O
ATOM	598	NE2	GLN	A	73	74.058	42.943	22.619	1.00	61.34	A	N
ATOM	599	N	GLY	A	74	73.591	46.763	18.223	1.00	48.16	A	N
ATOM	600	CA	GLY	A	74	74.262	48.041	18.020	1.00	42.89	A	C
ATOM	601	C	GLY	A	74	73.290	49.214	18.016	1.00	38.35	A	C
ATOM	602	O	GLY	A	74	72.224	49.115	18.625	1.00	39.09	A	O
ATOM	603	N	LYS	A	75	73.656	50.320	17.360	1.00	32.71	A	N
ATOM	604	CA	LYS	A	75	72.844	51.554	17.362	1.00	31.39	A	C
ATOM	605	C	LYS	A	75	73.525	52.762	16.664	1.00	24.85	A	C
ATOM	606	O	LYS	A	75	74.685	52.698	16.338	1.00	21.55	A	O
ATOM	607	CB	LYS	A	75	72.483	51.946	18.800	1.00	34.61	A	C
ATOM	608	CG	LYS	A	75	73.667	52.144	19.731	1.00	39.32	A	C
ATOM	609	CD	LYS	A	75	74.545	53.318	19.299	1.00	39.96	A	C
ATOM	610	CE	LYS	A	75	75.034	54.144	20.451	1.00	40.91	A	C
ATOM	611	NZ	LYS	A	75	74.297	55.407	20.464	1.00	45.34	A	N
ATOM	612	N	TRP	A	76	72.782	53.843	16.434	1.00	22.44	A	N
ATOM	613	CA	TRP	A	76	73.372	55.173	16.224	1.00	25.02	A	C

ATOM	614	C	TRP	A	76	72.594	56.201	17.012	1.00	23.16	A	C
ATOM	615	O	TRP	A	76	71.429	56.007	17.353	1.00	21.34	A	O
ATOM	616	CB	TRP	A	76	73.512	55.570	14.732	1.00	24.36	A	C
ATOM	617	CG	TRP	A	76	72.243	55.752	13.957	1.00	25.79	A	C
ATOM	618	CD1	TRP	A	76	71.643	54.833	13.136	1.00	26.34	A	C
ATOM	619	CD2	TRP	A	76	71.424	56.932	13.896	1.00	21.29	A	C
ATOM	620	NE1	TRP	A	76	70.491	55.364	12.595	1.00	27.23	A	N
ATOM	621	CE2	TRP	A	76	70.348	56.656	13.030	1.00	25.91	A	C
ATOM	622	CE3	TRP	A	76	71.497	58.202	14.479	1.00	24.01	A	C
ATOM	623	CZ2	TRP	A	76	69.349	57.595	12.752	1.00	26.87	A	C
ATOM	624	CZ3	TRP	A	76	70.512	59.124	14.202	1.00	26.34	A	C
ATOM	625	CH2	TRP	A	76	69.448	58.818	13.345	1.00	25.94	A	C
ATOM	626	N	GLU	A	77	73.291	57.271	17.354	1.00	22.20	A	N
ATOM	627	CA	GLU	A	77	72.753	58.327	18.164	1.00	24.84	A	C
ATOM	628	C	GLU	A	77	73.255	59.632	17.575	1.00	22.78	A	C
ATOM	629	O	GLU	A	77	74.386	59.723	17.089	1.00	19.61	A	O
ATOM	630	CB	GLU	A	77	73.214	58.140	19.621	1.00	28.88	A	C
ATOM	631	CG	GLU	A	77	72.959	59.331	20.529	1.00	35.35	A	C
ATOM	632	CD	GLU	A	77	73.323	59.057	21.980	0.50	36.38	A	C
ATOM	633	OE1	GLU	A	77	74.397	58.470	22.222	0.50	42.18	A	O
ATOM	634	OE2	GLU	A	77	72.536	59.431	22.878	0.50	39.02	A	O
ATOM	635	N	GLY	A	78	72.418	60.651	17.573	1.00	24.09	A	N
ATOM	636	CA	GLY	A	78	72.811	61.883	16.933	1.00	25.68	A	C
ATOM	637	C	GLY	A	78	72.160	63.134	17.453	1.00	25.43	A	C
ATOM	638	O	GLY	A	78	71.328	63.116	18.350	1.00	27.93	A	O
ATOM	639	N	GLU	A	79	72.579	64.234	16.861	1.00	23.79	A	N
ATOM	640	CA	GLU	A	79	72.078	65.542	17.187	1.00	23.88	A	C
ATOM	641	C	GLU	A	79	71.283	65.981	15.979	1.00	22.32	A	C
ATOM	642	O	GLU	A	79	71.800	65.979	14.875	1.00	26.62	A	O
ATOM	643	CB	GLU	A	79	73.255	66.487	17.457	1.00	23.99	A	C
ATOM	644	CG	GLU	A	79	74.109	66.052	18.641	1.00	29.60	A	C
ATOM	645	CD	GLU	A	79	75.420	66.826	18.790	1.00	33.85	A	C
ATOM	646	OE1	GLU	A	79	76.205	66.467	19.685	1.00	34.63	A	O
ATOM	647	OE2	GLU	A	79	75.670	67.782	18.030	1.00	37.21	A	O
ATOM	648	N	LEU	A	80	70.017	66.338	16.180	1.00	22.69	A	N
ATOM	649	CA	LEU	A	80	69.184	66.809	15.075	1.00	24.78	A	C
ATOM	650	C	LEU	A	80	69.419	68.267	14.685	1.00	26.56	A	C
ATOM	651	O	LEU	A	80	69.596	69.139	15.528	1.00	26.06	A	O
ATOM	652	CB	LEU	A	80	67.704	66.617	15.403	1.00	26.07	A	C
ATOM	653	CG	LEU	A	80	67.233	65.168	15.432	1.00	31.35	A	C
ATOM	654	CD1	LEU	A	80	65.863	65.082	16.077	1.00	28.71	A	C
ATOM	655	CD2	LEU	A	80	67.212	64.609	14.015	1.00	32.32	A	C
ATOM	656	N	GLY	A	81	69.390	68.525	13.383	1.00	23.46	A	N
ATOM	657	CA	GLY	A	81	69.500	69.861	12.822	1.00	22.46	A	C
ATOM	658	C	GLY	A	81	68.854	69.916	11.448	1.00	26.63	A	C
ATOM	659	O	GLY	A	81	68.308	68.927	11.002	1.00	22.44	A	O
ATOM	660	N	THR	A	82	68.884	71.065	10.787	1.00	26.31	A	N
ATOM	661	CA	THR	A	82	68.530	71.138	9.369.	1.00	28.52	A	C
ATOM	662	C	THR	A	82	69.634	71.813	8.631	1.00	25.22	A	C
ATOM	663	O	THR	A	82	70.436	72.529	9.225	1.00	27.82	A	O
ATOM	664	CB	THR	A	82	67.190	71.888	9.127	1.00	29.47	A	C
ATOM	665	OG1	THR	A	82	67.310	73.253	9.554	1.00	27.90	A	O
ATOM	666	CG2	THR	A	82	66.069	71.306	9.972	1.00	30.70	A	C
ATOM	667	N	ASP	A	83	69.704	71.567	7.326	1.00	24.75	A	N
ATOM	668	CA	ASP	A	83	70.679	72.180	6.447	1.00	22.11	A	C
ATOM	669	C	ASP	A	83	70.241	71.993	5.009	1.00	24.09	A	C
ATOM	670	O	ASP	A	83	69.261	71.285	4.741	1.00	26.17	A	O
ATOM	671	CB	ASP	A	83	72.075	71.559	6.652	1.00	24.10	A	C
ATOM	672	CG	ASP	A	83	73.213	72.542	6.376	1.00	26.19	A	C
ATOM	673	OD1	ASP	A	83	73.067	73.513	5.580	1.00	27.95	A	O
ATOM	674	OD2	ASP	A	83	74.328	72.409	6.924	1.00	25.64	A	O
ATOM	675	N	LEU	A	84	70.973	72.591	4.081	1.00	26.89	A	N
ATOM	676	CA	LEU	A	84	70.641	72.502	2.658	1.00	27.35	A	C
ATOM	677	C	LEU	A	84	71.224	71.225	2.078	1.00	28.51	A	C
ATOM	678	O	LEU	A	84	72.398	70.936	2.266	1.00	25.25	A	O
ATOM	679	CB	LEU	A	84	71.193	73.717	1.915	1.00	29.63	A	C
ATOM	680	CG	LEU	A	84	70.550	75.047	2.345	1.00	31.38	A	C
ATOM	681	CD1	LEU	A	84	71.025	76.228	1.501	1.00	30.45	A	C
ATOM	682	CD2	LEU	A	84	69.027	74.949	2.301	1.00	30.98	A	C
ATOM	683	N	VAL	A	85	70.392	70.465	1.373	1.00	25.49	A	N
ATOM	684	CA	VAL	A	85	70.790	69.203	0.768	1.00	28.08	A	C
ATOM	685	C	VAL	A	85	70.523	69.177	-0.737	1.00	27.65	A	C
ATOM	686	O	VAL	A	85	69.511	69.686	-1.213	1.00	27.43	A	O
ATOM	687	CB	VAL	A	85	70.063	68.028	1.439	1.00	27.18	A	C
ATOM	688	CG1	VAL	A	85	70.564	66.696	0.875	1.00	27.97	A	C
ATOM	689	CG2	VAL	A	85	70.273	68.084	2.950	1.00	29.93	A	C
ATOM	690	N	SER	A	86	71.451	68.587	-1.472	1.00	28.67	A	N

ATOM	691	CA	SER	A	86	71.331	68.409	-2.913	1.00	30.97	A	C
ATOM	692	C	SER	A	86	71.823	67.015	-3.293	1.00	31.51	A	C
ATOM	693	O	SER	A	86	72.512	66.354	-2.509	1.00	25.69	A	O
ATOM	694	CB	SER	A	86	72.138	69.485	-3.642	1.00	33.70	A	C
ATOM	695	OG	SER	A	86	71.607	69.737	-4.930	1.00	42.01	A	O
ATOM	696	N	ILE	A	87	71.459	66.563	-4.494	1.00	24.97	A	N
ATOM	697	CA	ILE	A	87	71.895	65.277	-5.006	1.00	25.75	A	C
ATOM	698	C	ILE	A	87	72.489	65.559	-6.384	1.00	29.06	A	C
ATOM	699	O	ILE	A	87	71.737	65.734	-7.354	1.00	27.25	A	O
ATOM	700	CB	ILE	A	87	70.713	64.275	-5.094	1.00	25.77	A	C
ATOM	701	CG1	ILE	A	87	70.062	64.090	-3.729	1.00	26.43	A	C
ATOM	702	CG2	ILE	A	87	71.187	62.939	-5.631	1.00	23.43	A	C
ATOM	703	CD1	ILE	A	87	68.758	63.332	-3.747	1.00	29.21	A	C
ATOM	704	N	PRO	A	88	73.817	65.654	-6.453	1.00	29.18	A	N
ATOM	705	CA	PRO	A	88	74.531	66.013	-7.689	1.00	30.76	A	C
ATOM	706	C	PRO	A	88	74.063	65.286	-8.956	1.00	32.20	A	C
ATOM	707	O	PRO	A	88	73.924	65.938	-9.987	1.00	33.45	A	O
ATOM	708	CB	PRO	A	88	75.971	65.632	-7.358	1.00	31.55	A	C
ATOM	709	CG	PRO	A	88	76.067	65.895	-5.896	1.00	30.46	A	C
ATOM	710	CD	PRO	A	88	74.762	65.455	-5.339	1.00	28.40	A	C
ATOM	711	N	HIS	A	89	73.857	63.972	-8.872	1.00	27.36	A	N
ATOM	712	CA	HIS	A	89	73.332	63.162	-9.978	1.00	28.26	A	C
ATOM	713	C	HIS	A	89	71.871	62.815	-9.715	1.00	29.29	A	C
ATOM	714	O	HIS	A	89	71.449	61.661	-9.847	1.00	28.09	A	O
ATOM	715	CB	HIS	A	89	74.173	61.907	-10.160	1.00	28.17	A	C
ATOM	716	CG	HIS	A	89	75.632	62.184	-10.362	1.00	38.05	A	C
ATOM	717	ND1	HIS	A	89	76.120	62.833	-11.478	1.00	41.06	A	N
ATOM	718	CD2	HIS	A	89	76.708	61.905	-9.588	1.00	38.74	A	C
ATOM	719	CE1	HIS	A	89	77.435	62.933	-11.384	1.00	40.63	A	C
ATOM	720	NE2	HIS	A	89	77.817	62.376	-10.248	1.00	41.19	A	N
ATOM	721	N	GLY	A	90	71.120	63.846	-9.334	1.00	32.50	A	N
ATOM	722	CA	GLY	A	90	69.696	63.769	-9.051	1.00	31.86	A	C
ATOM	723	C	GLY	A	90	69.005	64.963	-9.686	1.00	30.26	A	C
ATOM	724	O	GLY	A	90	69.524	65.524	-10.644	1.00	31.12	A	O
ATOM	725	N	PRO	A	91	67.861	65.382	-9.158	1.00	32.37	A	N
ATOM	726	CA	PRO	A	91	67.175	66.565	-9.691	1.00	34.88	A	C
ATOM	727	C	PRO	A	91	67.987	67.835	-9.410	1.00	39.91	A	C
ATOM	728	O	PRO	A	91	68.764	67.852	-8.458	1.00	38.58	A	O
ATOM	729	CB	PRO	A	91	65.837	66.579	-8.937	1.00	35.23	A	C
ATOM	730	CG	PRO	A	91	66.049	65.738	-7.711	1.00	34.49	A	C
ATOM	731	CD	PRO	A	91	67.164	64.807	-7.994	1.00	33.82	A	C
ATOM	732	N	ASN	A	92	67.809	68.863	-10.238	1.00	43.06	A	N
ATOM	733	CA	ASN	A	92	68.496	70.152	-10.086	1.00	45.05	A	C
ATOM	734	C	ASN	A	92	67.841	71.060	-9.034	1.00	44.59	A	C
ATOM	735	O	ASN	A	92	67.368	72.156	-9.337	1.00	44.08	A	O
ATOM	736	CB	ASN	A	92	68.546	70.860	-11.441	1.00	47.21	A	C
ATOM	737	CG	ASN	A	92	69.438	72.079	-11.431	1.00	50.71	A	C
ATOM	738	OD1	ASN	A	92	70.604	72.003	-11.044	1.00	52.68	A	O
ATOM	739	ND2	ASN	A	92	68.895	73.217	-11.863	1.00	52.24	A	N
ATOM	740	N	VAL	A	93	67.830	70.592	-7.789	1.00	41.78	A	N
ATOM	741	CA	VAL	A	93	67.205	71.310	-6.691	1.00	36.70	A	C
ATOM	742	C	VAL	A	93	68.043	71.217	-5.428	1.00	35.54	A	C
ATOM	743	O	VAL	A	93	68.907	70.353	-5.304	1.00	36.77	A	O
ATOM	744	CB	VAL	A	93	65.794	70.772	-6.374	1.00	38.91	A	C
ATOM	745	CG1	VAL	A	93	64.868	70.960	-7.573	1.00	37.74	A	C
ATOM	746	CG2	VAL	A	93	65.848	69.310	-5.921	1.00	37.34	A	C
ATOM	747	N	THR	A	94	67.772	72.139	-4.513	1.00	33.85	A	N
ATOM	748	CA	THR	A	94	68.320	72.119	-3.178	1.00	35.85	A	C
ATOM	749	C	THR	A	94	67.170	72.293	-2.216	1.00	36.41	A	C
ATOM	750	O	THR	A	94	66.283	73.119	-2.443	1.00	38.29	A	O
ATOM	751	CB	THR	A	94	69.327	73.252	-3.009	1.00	37.46	A	C
ATOM	752	OG1	THR	A	94	70.459	73.016	-3.855	1.00	37.95	A	O
ATOM	753	CG2	THR	A	94	69.910	73.256	-1.599	1.00	39.22	A	C
ATOM	754	N	VAL	A	95	67.162	71.515	-1.143	1.00	32.79	A	N
ATOM	755	CA	VAL	A	95	66.110	71.652	-0.155	1.00	32.68	A	C
ATOM	756	C	VAL	A	95	66.660	71.686	1.261	1.00	30.49	A	C
ATOM	757	O	VAL	A	95	67.762	71.240	1.499	1.00	31.56	A	O
ATOM	758	CB	VAL	A	95	65.071	70.544	-0.291	1.00	36.55	A	C
ATOM	759	CG1	VAL	A	95	64.479	70.568	-1.709	1.00	38.67	A	C
ATOM	760	CG2	VAL	A	95	65.663	69.183	0.025	1.00	33.09	A	C
ATOM	761	N	ARG	A	96	65.883	72.244	2.181	1.00	30.99	A	N
ATOM	762	CA	ARG	A	96	66.212	72.215	3.597	1.00	29.56	A	C
ATOM	763	C	ARG	A	96	65.620	70.957	4.208	1.00	28.73	A	C
ATOM	764	O	ARG	A	96	64.402	70.809	4.302	1.00	30.19	A	O
ATOM	765	CB	ARG	A	96	65.686	73.459	4.320	1.00	33.02	A	C
ATOM	766	CG	ARG	A	96	65.976	73.474	5.835	1.00	36.80	A	C
ATOM	767	CD	ARG	A	96	65.954	74.863	6.457	1.00	38.14	A	C

ATOM	768	NE	ARG	A	96	67.041	75.677	5.929	1.00	37.92	A	N
ATOM	769	CZ	ARG	A	96	68.265	75.747	6.442	1.00	37.97	A	C
ATOM	770	NH1	ARG	A	96	68.600	75.050	7.524	1.00	38.44	A	N
ATOM	771	NH2	ARG	A	96	69.160	76.512	5.846	1.00	33.62	A	N
ATOM	772	N	ALA	A	97	66.503	70.048	4.606	1.00	24.74	A	N
ATOM	773	CA	ALA	A	97	66.126	68.764	5.167	1.00	27.21	A	C
ATOM	774	C	ALA	A	97	66.541	68.668	6.614	1.00	22.38	A	C
ATOM	775	O	ALA	A	97	67.523	69.278	7.026	1.00	23.68	A	O
ATOM	776	CB	ALA	A	97	66.801	67.648	4.380	1.00	24.80	A	C
ATOM	777	N	ASN	A	98	65.796	67.884	7.378	1.00	21.67	A	N
ATOM	778	CA	ASN	A	98	66.281	67.388	8.644	1.00	22.81	A	C
ATOM	779	C	ASN	A	98	67.502	66.503	8.409	1.00	25.29	A	C
ATOM	780	O	ASN	A	98	67.538	65.738	7.451	1.00	21.43	A	O
ATOM	781	CB	ASN	A	98	65.184	66.605	9.351	1.00	23.87	A	C
ATOM	782	CG	ASN	A	98	64.033	67.503	9.805	1.00	31.55	A	C
ATOM	783	OD1	ASN	A	98	64.257	68.532	10.448	1.00	28.77	A	O
ATOM	784	ND2	ASN	A	98	62.801	67.115	9.469	1.00	29.01	A	N
ATOM	785	N	ILE	A	99	68.517	66.652	9.255	1.00	23.47	A	N
ATOM	786	CA	ILE	A	99	69.693	65.781	9.240	1.00	21.95	A	C
ATOM	787	C	ILE	A	99	70.048	65.437	10.685	1.00	19.63	A	C
ATOM	788	O	ILE	A	99	70.186	66.339	11.529	1.00	24.71	A	O
ATOM	789	CB	ILE	A	99	70.902	66.475	8.586	1.00	22.78	A	C
ATOM	790	CG1	ILE	A	99	70.571	66.968	7.184	1.00	19.57	A	C
ATOM	791	CG2	ILE	A	99	72.076	65.544	8.527	1.00	25.77	A	C
ATOM	792	CD1	ILE	A	99	71.663	67.806	6.568	1.00	26.04	A	C
ATOM	793	N	ALA	A	100	70.167	64.149	10.968	1.00	17.47	A	N
ATOM	794	CA	ALA	A	100	70.721	63.657	12.223	1.00	17.42	A	C
ATOM	795	C	ALA	A	100	72.245	63.532	12.075	1.00	21.54	A	C
ATOM	796	O	ALA	A	100	72.742	62.697	11.325	1.00	18.72	A	O
ATOM	797	CB	ALA	A	100	70.116	62.345	12.607	1.00	21.16	A	C
ATOM	798	N	ALA	A	101	72.981	64.369	12.804	1.00	18.65	A	N
ATOM	799	CA	ALA	A	101	74.436	64.308	12.819	1.00	19.52	A	C
ATOM	800	C	ALA	A	101	74.849	63.244	13.813	1.00	19.24	A	C
ATOM	801	O	ALA	A	101	74.595	63.358	15.017	1.00	22.30	A	O
ATOM	802	CB	ALA	A	101	75.052	65.702	13.163	1.00	21.40	A	C
ATOM	803	N	ILE	A	102	75.398	62.150	13.311	1.00	15.90	A	N
ATOM	804	CA	ILE	A	102	75.660	60.973	14.129	1.00	17.94	A	C
ATOM	805	C	ILE	A	102	76.952	61.245	14.892	1.00	19.52	A	C
ATOM	806	O	ILE	A	102	77.978	61.511	14.288	1.00	19.99	A	O
ATOM	807	CB	ILE	A	102	75.842	59.690	13.277	1.00	15.21	A	C
ATOM	808	CG1	ILE	A	102	74.554	59.374	12.505	1.00	16.99	A	C
ATOM	809	CG2	ILE	A	102	76.224	58.519	14.178	1.00	18.39	A	C
ATOM	810	CD1	ILE	A	102	74.673	58.276	11.472	1.00	19.74	A	C
ATOM	811	N	THR	A	103	76.866	61.146	16.212	1.00	21.46	A	N
ATOM	812	CA	THR	A	103	77.982	61.450	17.114	1.00	25.21	A	C
ATOM	813	C	THR	A	103	78.451	60.245	17.925	1.00	26.42	A	C
ATOM	814	O	THR	A	103	79.504	60.296	18.556	1.00	27.83	A	O
ATOM	815	CB	THR	A	103	77.556	62.579	18.073	1.00	24.52	A	C
ATOM	816	OG1	THR	A	103	76.344	62.216	18.746	1.00	26.84	A	O
ATOM	817	CG2	THR	A	103	77.183	63.831	17.317	1.00	25.79	A	C
ATOM	818	N	GLU	A	104	77.668	59.168	17.934	1.00	23.45	A	N
ATOM	819	CA	GLU	A	104	78.061	57.917	18.576	1.00	19.81	A	C
ATOM	820	C	GLU	A	104	77.351	56.767	17.877	1.00	21.65	A	C
ATOM	821	O	GLU	A	104	76.208	56.921	17.465	1.00	21.87	A	O
ATOM	822	CB	GLU	A	104	77.725	57.928	20.088	1.00	28.17	A	C
ATOM	823	CG	GLU	A	104	78.291	56.737	20.854	1.00	33.07	A	C
ATOM	824	CD	GLU	A	104	77.964	56.726	22.350	1.00	42.35	A	C
ATOM	825	OE1	GLU	A	104	77.594	57.785	22.928	1.00	48.99	A	O
ATOM	826	OE2	GLU	A	104	78.089	55.637	22.961	1.00	51.21	A	O
ATOM	827	N	SER	A	105	78.043	55.649	17.693	1.00	19.13	A	N
ATOM	828	CA	SER	A	105	77.446	54.481	17.026	1.00	20.88	A	C
ATOM	829	C	SER	A	105	78.126	53.167	17.421	1.00	24.82	A	C
ATOM	830	O	SER	A	105	79.260	53.151	17.929	1.00	23.75	A	O
ATOM	831	CB	SER	A	105	77.440	54.676	15.490	1.00	18.17	A	C
ATOM	832	OG	SER	A	105	78.758	54.663	15.012	1.00	21.83	A	O
ATOM	833	N	ASP	A	106	77.400	52.072	17.214	1.00	22.55	A	N
ATOM	834	CA	ASP	A	106	77.913	50.733	17.411	1.00	24.69	A	C
ATOM	835	C	ASP	A	106	77.315	49.839	16.312	1.00	23.68	A	C
ATOM	836	O	ASP	A	106	76.094	49.837	16.093	1.00	22.98	A	O
ATOM	837	CB	ASP	A	106	77.556	50.196	18.792	1.00	29.23	A	C
ATOM	838	CG	ASP	A	106	77.998	48.751	18.973	0.50	30.82	A	C
ATOM	839	OD1	ASP	A	106	79.136	48.520	19.419	0.50	35.18	A	O
ATOM	840	OD2	ASP	A	106	77.279	47.781	18.668	0.50	34.57	A	O
ATOM	841	N	LYS	A	107	78.190	49.123	15.618	1.00	25.54	A	N
ATOM	842	CA	LYS	A	107	77.820	48.161	14.572	1.00	22.36	A	C
ATOM	843	C	LYS	A	107	76.966	48.753	13.446	1.00	25.69	A	C
ATOM	844	O	LYS	A	107	76.176	48.054	12.825	1.00	22.57	A	O

ATOM	845	CB	LYS	A	107	77.139	46.935	15.195	1.00	27.43	A	C
ATOM	846	CG	LYS	A	107	78.066	46.130	16.101	1.00	32.24	A	C
ATOM	847	CD	LYS	A	107	77.314	45.034	16.835	1.00	33.50	A	C
ATOM	848	CE	LYS	A	107	78.004	44.328	17.899	0.00	31.63	A	C
ATOM	849	NZ	LYS	A	107	79.348	43.882	17.435	0.00	31.79	A	N
ATOM	850	N	PHE	A	108	77.151	50.043	13.187	1.00	22.67	A	N
ATOM	851	CA	PHE	A	108	76.412	50.770	12.161	1.00	20.97	A	C
ATOM	852	C	PHE	A	108	77.306	50.946	10.954	1.00	19.92	A	C
ATOM	853	O	PHE	A	108	77.016	50.416	9.875	1.00	21.69	A	O
ATOM	854	CB	PHE	A	108	75.946	52.125	12.691	1.00	19.57	A	C
ATOM	855	CG	PHE	A	108	75.153	52.921	11.701	1.00	20.66	A	C
ATOM	856	CD1	PHE	A	108	73.870	52.520	11.338	1.00	25.16	A	C
ATOM	857	CD2	PHE	A	108	75.688	54.053	11.107	1.00	22.61	A	C
ATOM	858	CE1	PHE	A	108	73.139	53.250	10.405	1.00	25.50	A	C
ATOM	859	CE2	PHE	A	108	74.963	54.790	10.190	1.00	22.84	A	C
ATOM	860	CZ	PHE	A	108	73.677	54.381	9.832	1.00	26.62	A	C
ATOM	861	N	PHE	A	109	78.401	51.682	11.129	1.00	20.35	A	N
ATOM	862	CA	PHE	A	109	79.372	51.887	10.044	1.00	20.96	A	C
ATOM	863	C	PHE	A	109	80.123	50.581	9.813	1.00	19.74	A	C
ATOM	864	O	PHE	A	109	80.361	49.824	10.769	1.00	24.70	A	O
ATOM	865	CB	PHE	A	109	80.325	53.065	10.348	1.00	19.85	A	C
ATOM	866	CG	PHE	A	109	79.617	54.398	10.489	1.00	16.19	A	C
ATOM	867	CD1	PHE	A	109	78.862	54.897	9.435	1.00	22.18	A	C
ATOM	868	CD2	PHE	A	109	79.726	55.162	11.633	1.00	22.85	A	C
ATOM	869	CE1	PHE	A	109	78.197	56.107	9.532	1.00	21.10	A	C
ATOM	870	CE2	PHE	A	109	79.066	56.377	11.728	1.00	21.43	A	C
ATOM	871	CZ	PHE	A	109	78.284	56.841	10.663	1.00	22.40	A	C
ATOM	872	N	ILE	A	110	80.460	50.285	8.556	1.00	24.38	A	N
ATOM	873	CA	ILE	A	110	81.176	49.060	8.204	1.00	23.73	A	C
ATOM	874	C	ILE	A	110	82.627	49.382	7.863	1.00	25.17	A	C
ATOM	875	O	ILE	A	110	82.917	50.295	7.077	1.00	21.65	A	O
ATOM	876	CB	ILE	A	110	80.510	48.364	6.998	1.00	23.43	A	C
ATOM	877	CG1	ILE	A	110	79.073	47.944	7.330	1.00	26.13	A	C
ATOM	878	CG2	ILE	A	110	81.354	47.171	6.511	1.00	27.63	A	C
ATOM	879	CD1	ILE	A	110	78.262	47.542	6.104	1.00	29.01	A	C
ATOM	880	N	ASN	A	111	83.535	48.616	8.453	1.00	24.01	A	N
ATOM	881	CA	ASN	A	111	84.958	48.786	8.213	1.00	25.66	A	C
ATOM	882	C	ASN	A	111	85.302	48.367	6.782	1.00	21.62	A	C
ATOM	883	O	ASN	A	111	85.122	47.210	6.395	1.00	24.50	A	O
ATOM	884	CB	ASN	A	111	85.762	47.950	9.219	1.00	26.77	A	C
ATOM	885	CG	ASN	A	111	87.239	48.324	9.252	1.00	30.39	A	C
ATOM	886	OD1	ASN	A	111	87.614	49.478	9.012	1.00	29.76	A	O
ATOM	887	ND2	ASN	A	111	88.081	47.348	9.588	1.00	28.98	A	N
ATOM	888	N	GLY	A	112	85.815	49.310	6.008	1.00	21.53	A	N
ATOM	889	CA	GLY	A	112	86.127	49.082	4.604	1.00	26.83	A	C
ATOM	890	C	GLY	A	112	85.073	49.602	3.630	1.00	27.54	A	C
ATOM	891	O	GLY	A	112	85.274	49.562	2.419	1.00	26.87	A	O
ATOM	892	N	SER	A	113	83.950	50.086	4.145	1.00	28.16	A	N
ATOM	893	CA	SER	A	113	82.869	50.607	3.301	1.00	23.29	A	C
ATOM	894	C	SER	A	113	83.152	52.034	2.864	1.00	22.88	A	C
ATOM	895	O	SER	A	113	83.981	52.730	3.462	1.00	22.23	A	O
ATOM	896	CB	SER	A	113	81.537	50.544	4.053	1.00	26.77	A	C
ATOM	897	OG	SER	A	113	81.450	51.622	4.968	1.00	32.46	A	O
ATOM	898	N	ASN	A	114	82.451	52.469	1.818	1.00	19.83	A	N
ATOM	899	CA	ASN	A	114	82.632	53.785	1.195	1.00	20.70	A	C
ATOM	900	C	ASN	A	114	81.400	54.686	1.349	1.00	17.94	A	C
ATOM	901	O	ASN	A	114	81.228	55.627	0.596	1.00	20.08	A	O
ATOM	902	CB	ASN	A	114	82.973	53.574	-0.303	1.00	20.54	A	C
ATOM	903	CG	ASN	A	114	83.533	54.827	-1.004	1.00	26.09	A	C
ATOM	904	OD1	ASN	A	114	83.189	55.100	-2.165	1.00	29.37	A	O
ATOM	905	ND2	ASN	A	114	84.441	55.540	-0.348	1.00	22.18	A	N
ATOM	906	N	TRP	A	115	80.558	54.414	2.354	1.00	16.89	A	N
ATOM	907	CA	TRP	A	115	79.453	55.295	2.658	1.00	16.46	A	C
ATOM	908	C	TRP	A	115	79.548	55.772	4.100	1.00	18.12	A	C
ATOM	909	O	TRP	A	115	80.184	55.126	4.943	1.00	20.65	A	O
ATOM	910	CB	TRP	A	115	78.093	54.631	2.393	1.00	18.60	A	C
ATOM	911	CG	TRP	A	115	77.869	53.335	3.061	1.00	18.81	A	C
ATOM	912	CD1	TRP	A	115	78.058	52.098	2.520	1.00	27.02	A	C
ATOM	913	CD2	TRP	A	115	77.372	53.109	4.403	1.00	19.85	A	C
ATOM	914	NE1	TRP	A	115	77.734	51.123	3.434	1.00	28.07	A	N
ATOM	915	CE2	TRP	A	115	77.311	51.716	4.597	1.00	28.04	A	C
ATOM	916	CE3	TRP	A	115	76.983	53.943	5.453	1.00	21.36	A	C
ATOM	917	CZ2	TRP	A	115	76.877	51.142	5.799	1.00	27.30	A	C
ATOM	918	CZ3	TRP	A	115	76.544	53.371	6.643	1.00	22.49	A	C
ATOM	919	CH2	TRP	A	115	76.510	51.996	6.808	1.00	24.66	A	C
ATOM	920	N	GLU	A	116	78.910	56.905	4.345	1.00	18.09	A	N
ATOM	921	CA	GLU	A	116	79.049	57.666	5.584	1.00	18.37	A	C

ATOM	922	C	GLU	A	116	77.726	58.110	6.220	1.00	21.39	A	C
ATOM	923	O	GLU	A	116	77.719	58.866	7.185	1.00	19.69	A	O
ATOM	924	CB	GLU	A	116	79.891	58.924	5.282	1.00	21.09	A	C
ATOM	925	CG	GLU	A	116	81.298	58.664	4.834	1.00	30.57	A	C
ATOM	926	CD	GLU	A	116	81.495	58.683	3.331	1.00	19.12	A	C
ATOM	927	OE1	GLU	A	116	80.945	59.571	2.609	1.00	25.47	A	O
ATOM	928	OE2	GLU	A	116	82.237	57.811	2.889	1.00	30.78	A	O
ATOM	929	N	GLY	A	117	76.601	57.670	5.680	1.00	15.48	A	N
ATOM	930	CA	GLY	A	117	75.302	58.008	6.218	1.00	14.95	A	C
ATOM	931	C	GLY	A	117	74.221	57.194	5.523	1.00	17.22	A	C
ATOM	932	O	GLY	A	117	74.517	56.329	4.686	1.00	15.79	A	O
ATOM	933	N	ILE	A	118	72.980	57.475	5.888	1.00	18.20	A	N
ATOM	934	CA	ILE	A	118	71.810	56.721	5.455	1.00	12.85	A	C
ATOM	935	C	ILE	A	118	70.668	57.692	5.108	1.00	15.45	A	C
ATOM	936	O	ILE	A	118	70.426	58.691	5.805	1.00	15.49	A	O
ATOM	937	CB	ILE	A	118	71.401	55.687	6.518	1.00	16.49	A	C
ATOM	938	CG1	ILE	A	118	70.260	54.788	6.018	1.00	20.60	A	C
ATOM	939	CG2	ILE	A	118	70.977	56.368	7.820	1.00	18.54	A	C
ATOM	940	CD1	ILE	A	118	69.959	53.672	6.975	1.00	22.49	A	C
ATOM	941	N	LEU	A	119	69.973	57.386	4.012	1.00	16.51	A	N
ATOM	942	CA	LEU	A	119	68.850	58.180	3.520	1.00	17.34	A	C
ATOM	943	C	LEU	A	119	67.605	57.332	3.631	1.00	17.57	A	C
ATOM	944	O	LEU	A	119	67.370	56.426	2.823	1.00	17.07	A	O
ATOM	945	CB	LEU	A	119	69.061	58.614	2.073	1.00	16.12	A	C
ATOM	946	CG	LEU	A	119	67.954	59.469	1.461	1.00	20.50	A	C
ATOM	947	CD1	LEU	A	119	67.744	60.734	2.237	1.00	21.51	A	C
ATOM	948	CD2	LEU	A	119	68.286	59.797	0.034	1.00	22.00	A	C
ATOM	949	N	GLY	A	120	66.817	57.600	4.659	1.00	15.26	A	N
ATOM	950	CA	GLY	A	120	65.590	56.864	4.892	1.00	16.17	A	C
ATOM	951	C	GLY	A	120	64.506	57.419	3.975	1.00	16.03	A	C
ATOM	952	O	GLY	A	120	64.131	58.593	4.102	1.00	20.14	A	O
ATOM	953	N	LEU	A	121	64.011	56.582	3.064	1.00	15.98	A	N
ATOM	954	CA	LEU	A	121	63.037	57.010	2.038	1.00	16.93	A	C
ATOM	955	C	LEU	A	121	61.586	56.616	2.330	1.00	18.71	A	C
ATOM	956	O	LEU	A	121	60.683	56.874	1.530	1.00	20.26	A	O
ATOM	957	CB	LEU	A	121	63.460	56.449	0.682	1.00	16.32	A	C
ATOM	958	CG	LEU	A	121	64.699	57.128	0.084	1.00	18.18	A	C
ATOM	959	CD1	LEU	A	121	65.208	56.418	-1.167	1.00	17.74	A	C
ATOM	960	CD2	LEU	A	121	64.505	58.626	-0.230	1.00	19.83	A	C
ATOM	961	N	ALA	A	122	61.377	55.931	3.440	1.00	17.96	A	N
ATOM	962	CA	ALA	A	122	60.037	55.568	3.916	1.00	19.62	A	C
ATOM	963	C	ALA	A	122	59.307	56.740	4.589	1.00	24.01	A	C
ATOM	964	O	ALA	A	122	59.734	57.890	4.476	1.00	24.71	A	O
ATOM	965	CB	ALA	A	122	60.130	54.361	4.829	1.00	20.17	A	C
ATOM	966	N	TYR	A	123	58.185	56.447	5.256	1.00	23.30	A	N
ATOM	967	CA	TYR	A	123	57.265	57.473	5.703	1.00	25.93	A	C
ATOM	968	C	TYR	A	123	57.492	57.894	7.163	1.00	23.41	A	C
ATOM	969	O	TYR	A	123	58.146	57.192	7.931	1.00	25.28	A	O
ATOM	970	CB	TYR	A	123	55.836	56.968	5.559	1.00	25.54	A	C
ATOM	971	CG	TYR	A	123	55.441	56.697	4.129	1.00	24.32	A	C
ATOM	972	CD1	TYR	A	123	55.015	57.724	3.310	1.00	25.79	A	C
ATOM	973	CD2	TYR	A	123	55.491	55.421	3.609	1.00	26.50	A	C
ATOM	974	CE1	TYR	A	123	54.622	57.486	1.998	1.00	28.42	A	C
ATOM	975	CE2	TYR	A	123	55.120	55.171	2.293	1.00	27.28	A	C
ATOM	976	CZ	TYR	A	123	54.678	56.195	1.501	1.00	25.25	A	C
ATOM	977	OH	TYR	A	123	54.315	55.950	0.184	1.00	26.89	A	O
ATOM	978	N	ALA	A	124	56.879	59.014	7.519	1.00	29.24	A	N
ATOM	979	CA	ALA	A	124	57.082	59.664	8.820	1.00	30.24	A	C
ATOM	980	C	ALA	A	124	56.708	58.812	10.018	1.00	35.27	A	C
ATOM	981	O	ALA	A	124	57.302	58.953	11.091	1.00	33.99	A	O
ATOM	982	CB	ALA	A	124	56.356	60.972	8.858	1.00	31.62	A	C
ATOM	983	N	GLU	A	125	55.754	57.903	9.834	1.00	34.28	A	N
ATOM	984	CA	GLU	A	125	55.295	57.003	10.894	1.00	37.92	A	C
ATOM	985	C	GLU	A	125	56.415	56.274	11.647	1.00	37.65	A	C
ATOM	986	O	GLU	A	125	56.299	56.030	12.853	1.00	38.82	A	O
ATOM	987	CB	GLU	A	125	54.330	55.968	10.293	1.00	40.24	A	C
ATOM	988	CG	GLU	A	125	53.444	55.252	11.295	1.00	45.50	A	C
ATOM	989	CD	GLU	A	125	52.121	55.962	11.496	1.00	52.07	A	C
ATOM	990	OE1	GLU	A	125	52.131	57.123	11.977	1.00	54.94	A	O
ATOM	991	OE2	GLU	A	125	51.075	55.364	11.163	1.00	57.37	A	O
ATOM	992	N	ILE	A	126	57.491	55.918	10.941	1.00	31.63	A	N
ATOM	993	CA	ILE	A	126	58.585	55.155	11.525	1.00	28.26	A	C
ATOM	994	C	ILE	A	126	59.866	55.991	11.687	1.00	26.21	A	C
ATOM	995	O	ILE	A	126	60.920	55.440	11.948	1.00	28.24	A	O
ATOM	996	CB	ILE	A	126	58.878	53.883	10.690	1.00	31.52	A	C
ATOM	997	CG1	ILE	A	126	59.197	54.235	9.234	1.00	28.75	A	C
ATOM	998	CG2	ILE	A	126	57.699	52.908	10.764	1.00	31.40	A	C

ATOM	999	CD1	ILE	A	126	59.677	53.053	8.429	1.00	29.82	A	C
ATOM	1000	N	ALA	A	127	59.751	57.298	11.493	1.00	26.38	A	N
ATOM	1001	CA	ALA	A	127	60.844	58.222	11.762	1.00	28.14	A	C
ATOM	1002	C	ALA	A	127	61.072	58.286	13.267	1.00	30.57	A	C
ATOM	1003	O	ALA	A	127	60.139	58.129	14.056	1.00	27.34	A	O
ATOM	1004	CB	ALA	A	127	60.516	59.588	11.228	1.00	26.20	A	C
ATOM	1005	N	ARG	A	128	62.323	58.479	13.650	1.00	32.29	A	N
ATOM	1006	CA	ARG	A	128	62.686	58.711	15.042	1.00	32.33	A	C
ATOM	1007	C	ARG	A	128	63.110	60.172	15.214	1.00	32.76	A	C
ATOM	1008	O	ARG	A	128	63.673	60.773	14.288	1.00	28.12	A	O
ATOM	1009	CB	ARG	A	128	63.775	57.748	15.468	1.00	33.84	A	C
ATOM	1010	CG	ARG	A	128	63.268	56.329	15.638	1.00	39.19	A	C
ATOM	1011	CD	ARG	A	128	64.006	55.302	14.843	1.00	43.32	A	C
ATOM	1012	NE	ARG	A	128	63.338	54.007	14.915	1.00	49.88	A	N
ATOM	1013	CZ	ARG	A	128	63.811	52.881	14.384	1.00	49.47	A	C
ATOM	1014	NH1	ARG	A	128	63.115	51.757	14.508	1.00	52.74	A	N
ATOM	1015	NH2	ARG	A	128	64.968	52.865	13.731	1.00	50.48	A	N
ATOM	1016	N	PRO	A	129	62.816	60.791	16.364	1.00	31.47	A	N
ATOM	1017	CA	PRO	A	129	62.218	60.159	17.553	1.00	34.71	A	C
ATOM	1018	C	PRO	A	129	60.705	59.942	17.479	1.00	34.15	A	C
ATOM	1019	O	PRO	A	129	60.172	59.122	18.229	1.00	37.59	A	O
ATOM	1020	CB	PRO	A	129	62.498	61.176	18.670	1.00	32.03	A	C
ATOM	1021	CG	PRO	A	129	62.887	62.461	18.005	1.00	33.32	A	C
ATOM	1022	CD	PRO	A	129	63.036	62.232	16.548	1.00	34.13	A	C
ATOM	1023	N	ASP	A	130	60.031	60.701	16.626	1.00	34.80	A	N
ATOM	1024	CA	ASP	A	130	58.604	60.519	16.390	1.00	38.13	A	C
ATOM	1025	C	ASP	A	130	58.234	60.967	14.976	1.00	36.50	A	C
ATOM	1026	O	ASP	A	130	59.075	61.471	14.227	1.00	36.70	A	O
ATOM	1027	CB	ASP	A	130	57.779	61.280	17.450	1.00	39.51	A	C
ATOM	1028	CG	ASP	A	130	58.154	62.756	17.558	1.00	44.22	A	C
ATOM	1029	OD1	ASP	A	130	58.795	63.139	18.571	1.00	51.20	A	O
ATOM	1030	OD2	ASP	A	130	57.839	63.614	16.705	1.00	44.98	A	O
ATOM	1031	N	ASP	A	131	56.963	60.814	14.623	1.00	38.18	A	N
ATOM	1032	CA	ASP	A	131	56.511	61.090	13.261	1.00	38.88	A	C
ATOM	1033	C	ASP	A	131	56.397	62.569	12.911	1.00	36.53	A	C
ATOM	1034	O	ASP	A	131	55.943	62.905	11.827	1.00	35.45	A	O
ATOM	1035	CB	ASP	A	131	55.191	60.346	12.950	1.00	39.38	A	C
ATOM	1036	CG	ASP	A	131	54.010	60.844	13.771	1.00	41.70	A	C
ATOM	1037	OD1	ASP	A	131	54.067	61.976	14.296	1.00	42.89	A	O
ATOM	1038	OD2	ASP	A	131	52.970	60.165	13.935	1.00	42.85	A	O
ATOM	1039	N	SER	A	132	56.801	63.462	13.815	1.00	37.22	A	N
ATOM	1040	CA	SER	A	132	56.825	64.891	13.495	1.00	34.53	A	C
ATOM	1041	C	SER	A	132	58.138	65.313	12.811	1.00	32.93	A	C
ATOM	1042	O	SER	A	132	58.242	66.415	12.301	1.00	31.50	A	O
ATOM	1043	CB	SER	A	132	56.569	65.733	14.753	1.00	36.86	A	C
ATOM	1044	OG	SER	A	132	57.784	66.236	15.282	1.00	41.97	A	O
ATOM	1045	N	LEU	A	133	59.142	64.442	12.800	1.00	33.79	A	N
ATOM	1046	CA	LEU	A	133	60.371	64.730	12.053	1.00	32.04	A	C
ATOM	1047	C	LEU	A	133	60.174	64.308	10.601	1.00	30.10	A	C
ATOM	1048	O	LEU	A	133	60.179	63.117	10.279	1.00	31.31	A	O
ATOM	1049	CB	LEU	A	133	61.586	64.035	12.652	1.00	30.30	A	C
ATOM	1050	CG	LEU	A	133	62.901	64.622	12.116	1.00	31.05	A	C
ATOM	1051	CD1	LEU	A	133	63.289	65.900	12.891	1.00	30.64	A	C
ATOM	1052	CD2	LEU	A	133	64.000	63.606	12.180	1.00	26.23	A	C
ATOM	1053	N	GLU	A	134	60.028	65.294	9.734	1.00	32.24	A	N
ATOM	1054	CA	GLU	A	134	59.630	65.044	8.362	1.00	30.89	A	C
ATOM	1055	C	GLU	A	134	60.812	64.398	7.611	1.00	30.52	A	C
ATOM	1056	O	GLU	A	134	61.938	64.919	7.650	1.00	27.23	A	O
ATOM	1057	CB	GLU	A	134	59.088	66.332	7.709	1.00	35.75	A	C
ATOM	1058	CG	GLU	A	134	59.723	66.804	6.414	1.00	41.00	A	C
ATOM	1059	CD	GLU	A	134	59.016	68.022	5.819	1.00	43.25	A	C
ATOM	1060	OE1	GLU	A	134	59.719	68.930	5.302	1.00	45.72	A	O
ATOM	1061	OE2	GLU	A	134	57.763	68.096	5.869	1.00	48.16	A	O
ATOM	1062	N	PRO	A	135	60.566	63.249	6.975	1.00	25.18	A	N
ATOM	1063	CA	PRO	A	135	61.581	62.606	6.119	1.00	24.30	A	C
ATOM	1064	C	PRO	A	135	62.039	63.453	4.958	1.00	19.94	A	C
ATOM	1065	O	PRO	A	135	61.337	64.319	4.481	1.00	23.86	A	O
ATOM	1066	CB	PRO	A	135	60.847	61.379	5.579	1.00	22.83	A	C
ATOM	1067	CG	PRO	A	135	59.796	61.109	6.573	1.00	25.70	A	C
ATOM	1068	CD	PRO	A	135	59.328	62.450	7.020	1.00	24.61	A	C
ATOM	1069	N	PHE	A	136	63.243	63.160	4.474	1.00	19.75	A	N
ATOM	1070	CA	PHE	A	136	63.850	63.848	3.367	1.00	20.77	A	C
ATOM	1071	C	PHE	A	136	62.945	64.000	2.166	1.00	25.10	A	C
ATOM	1072	O	PHE	A	136	62.798	65.099	1.632	1.00	23.63	A	O
ATOM	1073	CB	PHE	A	136	65.094	63.106	2.886	1.00	21.20	A	C
ATOM	1074	CG	PHE	A	136	65.704	63.716	1.669	1.00	19.23	A	C
ATOM	1075	CD1	PHE	A	136	66.414	64.905	1.758	1.00	26.30	A	C

ATOM	1076	CD2	PHE	A	136	65.522	63.144	0.421	1.00	23.32	A	C
ATOM	1077	CE1	PHE	A	136	66.962	65.494	0.626	1.00	25.62	A	C
ATOM	1078	CE2	PHE	A	136	66.078	63.727	-0.719	1.00	23.61	A	C
ATOM	1079	CZ	PHE	A	136	66.787	64.903	-0.615	1.00	29.48	A	C
ATOM	1080	N	PHE	A	137	62.402	62.886	1.694	1.00	21.94	A	N
ATOM	1081	CA	PHE	A	137	61.655	62.903	0.444	1.00	20.25	A	C
ATOM	1082	C	PHE	A	137	60.396	63.749	0.582	1.00	21.90	A	C
ATOM	1083	O	PHE	A	137	59.966	64.370	-0.379	1.00	24.14	A	O
ATOM	1084	CB	PHE	A	137	61.271	61.509	-0.026	1.00	18.67	A	C
ATOM	1085	CG	PHE	A	137	61.039	61.440	-1.491	1.00	20.54	A	C
ATOM	1086	CD1	PHE	A	137	62.099	61.302	-2.361	1.00	23.22	A	C
ATOM	1087	CD2	PHE	A	137	59.757	61.511	-2.003	1.00	22.93	A	C
ATOM	1088	CE1	PHE	A	137	61.900	61.241	-3.721	1.00	27.68	A	C
ATOM	1089	CE2	PHE	A	137	59.551	61.462	-3.374	1.00	20.33	A	C
ATOM	1090	CZ	PHE	A	137	60.616	61.334	-4.232	1.00	22.33	A	C
ATOM	1091	N	ASP	A	138	59.814	63.750	1.775	1.00	22.45	A	N
ATOM	1092	CA	ASP	A	138	58.649	64.582	2.081	1.00	25.79	A	C
ATOM	1093	C	ASP	A	138	59.020	66.055	1.966	1.00	27.43	A	C
ATOM	1094	O	ASP	A	138	58.296	66.825	1.326	1.00	30.80	A	O
ATOM	1095	CB	ASP	A	138	58.124	64.309	3.479	1.00	27.52	A	C
ATOM	1096	CG	ASP	A	138	57.419	62.982	3.596	1.00	33.12	A	C
ATOM	1097	OD1	ASP	A	138	56.177	63.001	3.674	1.00	41.90	A	O
ATOM	1098	OD2	ASP	A	138	58.004	61.870	3.644	1.00	36.84	A	O
ATOM	1099	N	SER	A	139	60.141	66.452	2.573	1.00	25.82	A	N
ATOM	1100	CA	SER	A	139	60.662	67.825	2.393	1.00	26.28	A	C
ATOM	1101	C	SER	A	139	60.957	68.169	0.940	1.00	26.44	A	C
ATOM	1102	O	SER	A	139	60.719	69.293	0.496	1.00	28.87	A	O
ATOM	1103	CB	SER	A	139	61.951	68.049	3.204	1.00	21.06	A	C
ATOM	1104	OG	SER	A	139	61.769	67.663	4.541	1.00	25.91	A	O
ATOM	1105	N	LEU	A	140	61.493	67.212	0.188	1.00	24.71	A	N
ATOM	1106	CA	LEU	A	140	61.816	67.443	-1.209	1.00	24.32	A	C
ATOM	1107	C	LEU	A	140	60.547	67.732	-2.019	1.00	26.78	A	C
ATOM	1108	O	LEU	A	140	60.555	68.649	-2.851	1.00	28.93	A	O
ATOM	1109	CB	LEU	A	140	62.555	66.253	-1.819	1.00	25.33	A	C
ATOM	1110	CG	LEU	A	140	62.797	66.212	-3.332	1.00	27.48	A	C
ATOM	1111	CD1	LEU	A	140	63.903	67.142	-3.762	1.00	30.78	A	C
ATOM	1112	CD2	LEU	A	140	63.124	64.795	-3.764	1.00	32.40	A	C
ATOM	1113	N	VAL	A	141	59.482	66.964	-1.774	1.00	27.82	A	N
ATOM	1114	CA	VAL	A	141	58.236	67.121	-2.539	1.00	27.51	A	C
ATOM	1115	C	VAL	A	141	57.548	68.440	-2.159	1.00	33.11	A	C
ATOM	1116	O	VAL	A	141	57.054	69.159	-3.024	1.00	34.42	A	O
ATOM	1117	CB	VAL	A	141	57.268	65.953	-2.319	1.00	30.35	A	C
ATOM	1118	CG1	VAL	A	141	55.923	66.224	-2.980	1.00	31.75	A	C
ATOM	1119	CG2	VAL	A	141	57.849	64.666	-2.885	1.00	30.79	A	C
ATOM	1120	N	LYS	A	142	57.541	68.747	-0.868	1.00	32.37	A	N
ATOM	1121	CA	LYS	A	142	56.876	69.931	-0.338	1.00	37.06	A	C
ATOM	1122	C	LYS	A	142	57.527	71.211	-0.828	1.00	34.32	A	C
ATOM	1123	O	LYS	A	142	56.826	72.191	-1.091	1.00	35.77	A	O
ATOM	1124	CB	LYS	A	142	56.876	69.897	1.187	1.00	37.65	A	C
ATOM	1125	CG	LYS	A	142	56.135	71.055	1.850	1.00	44.63	A	C
ATOM	1126	CD	LYS	A	142	55.689	70.702	3.264	1.00	46.28	A	C
ATOM	1127	CE	LYS	A	142	54.644	71.684	3.779	1.00	49.93	A	C
ATOM	1128	NZ	LYS	A	142	54.400	71.364	5.250	0.00	45.29	A	N
ATOM	1129	N	GLN	A	143	58.848	71.196	-0.999	1.00	30.71	A	N
ATOM	1130	CA	GLN	A	143	59.602	72.415	-1.260	1.00	32.98	A	C
ATOM	1131	C	GLN	A	143	59.948	72.655	-2.726	1.00	31.39	A	C
ATOM	1132	O	GLN	A	143	60.393	73.754	-3.071	1.00	35.65	A	O
ATOM	1133	CB	GLN	A	143	60.900	72.429	-0.443	1.00	29.67	A	C
ATOM	1134	CG	GLN	A	143	60.712	72.505	1.045	1.00	29.86	A	C
ATOM	1135	CD	GLN	A	143	62.033	72.359	1.785	1.00	22.99	A	C
ATOM	1136	OE1	GLN	A	143	62.072	71.774	2.871	1.00	32.84	A	O
ATOM	1137	NE2	GLN	A	143	63.100	72.879	1.202	1.00	24.10	A	N
ATOM	1138	N	THR	A	144	59.767	71.650	-3.588	1.00	30.44	A	N
ATOM	1139	CA	THR	A	144	60.095	71.786	-5.011	1.00	31.63	A	C
ATOM	1140	C	THR	A	144	58.950	71.268	-5.887	1.00	32.37	A	C
ATOM	1141	O	THR	A	144	57.910	70.882	-5.368	1.00	35.67	A	O
ATOM	1142	CB	THR	A	144	61.405	71.032	-5.365	1.00	35.08	A	C
ATOM	1143	OG1	THR	A	144	61.169	69.613	-5.395	1.00	34.32	A	O
ATOM	1144	CG2	THR	A	144	62.458	71.221	-4.298	1.00	34.68	A	C
ATOM	1145	N	HIS	A	145	59.165	71.247	-7.203	1.00	36.14	A	N
ATOM	1146	CA	HIS	A	145	58.193	70.682	-8.155	1.00	39.38	A	C
ATOM	1147	C	HIS	A	145	58.512	69.232	-8.562	1.00	37.43	A	C
ATOM	1148	O	HIS	A	145	57.961	68.715	-9.544	1.00	33.33	A	O
ATOM	1149	CB	HIS	A	145	58.097	71.563	-9.409	1.00	43.05	A	C
ATOM	1150	CG	HIS	A	145	57.493	72.910	-9.154	1.00	47.15	A	C
ATOM	1151	ND1	HIS	A	145	56.200	73.072	-8.703	1.00	50.46	A	N
ATOM	1152	CD2	HIS	A	145	58.006	74.157	-9.284	1.00	49.69	A	C

ATOM	1153	CE1	HIS	A	145	55.941	74.361	-8.570	1.00	51.63	A	C
ATOM	1154	NE2	HIS	A	145	57.021	75.041	-8.913	1.00	51.86	A	N
ATOM	1155	N	VAL	A	146	59.379	68.565	-7.798	1.00	33.76	A	N
ATOM	1156	CA	VAL	A	146	59.705	67.163	-8.059	1.00	29.14	A	C
ATOM	1157	C	VAL	A	146	58.472	66.301	-7.774	1.00	22.43	A	C
ATOM	1158	O	VAL	A	146	57.885	66.398	-6.697	1.00	24.83	A	O
ATOM	1159	CB	VAL	A	146	60.921	66.695	-7.206	1.00	27.14	A	C
ATOM	1160	CG1	VAL	A	146	61.151	65.185	-7.339	1.00	27.28	A	C
ATOM	1161	CG2	VAL	A	146	62.178	67.468	-7.626	1.00	26.85	A	C
ATOM	1162	N	PRO	A	147	58.045	65.483	-8.744	1.00	26.48	A	N
ATOM	1163	CA	PRO	A	147	56.864	64.637	-8.557	1.00	26.08	A	C
ATOM	1164	C	PRO	A	147	57.049	63.662	-7.403	1.00	22.97	A	C
ATOM	1165	O	PRO	A	147	58.185	63.217	-7.166	1.00	27.41	A	O
ATOM	1166	CB	PRO	A	147	56.749	63.885	-9.882	1.00	25.30	A	C
ATOM	1167	CG	PRO	A	147	57.462	64.717	-10.865	1.00	27.21	A	C
ATOM	1168	CD	PRO	A	147	58.636	65.310	-10.089	1.00	25.24	A	C
ATOM	1169	N	ASN	A	148	55.963	63.339	-6.711	1.00	21.69	A	N
ATOM	1170	CA	ASN	A	148	56.014	62.466	-5.551	1.00	21.05	A	C
ATOM	1171	C	ASN	A	148	56.167	60.969	-5.908	1.00	21.77	A	C
ATOM	1172	O	ASN	A	148	55.305	60.152	-5.607	1.00	21.62	A	O
ATOM	1173	CB	ASN	A	148	54.797	62.717	-4.670	1.00	23.86	A	C
ATOM	1174	CG	ASN	A	148	54.878	62.024	-3.338	1.00	22.10	A	C
ATOM	1175	OD1	ASN	A	148	55.967	61.652	-2.885	1.00	20.69	A	O
ATOM	1176	ND2	ASN	A	148	53.716	61.795	-2.710	1.00	25.43	A	N
ATOM	1177	N	LEU	A	149	57.291	60.629	-6.524	1.00	20.43	A	N
ATOM	1178	CA	LEU	A	149	57.666	59.252	-6.775	1.00	22.50	A	C
ATOM	1179	C	LEU	A	149	59.152	59.110	-7.020	1.00	21.20	A	C
ATOM	1180	O	LEU	A	149	59.838	60.073	-7.389	1.00	19.54	A	O
ATOM	1181	CB	LEU	A	149	56.859	58.654	-7.927	1.00	25.03	A	C
ATOM	1182	CG	LEU	A	149	57.349	58.789	-9.346	1.00	28.60	A	C
ATOM	1183	CD1	LEU	A	149	56.502	57.899	-10.267	1.00	30.70	A	C
ATOM	1184	CD2	LEU	A	149	57.237	60.237	-9.725	1.00	30.68	A	C
ATOM	1185	N	PHE	A	150	59.678	57.919	-6.745	1.00	18.27	A	N
ATOM	1186	CA	PHE	A	150	61.044	57.586	-7.149	1.00	18.21	A	C
ATOM	1187	C	PHE	A	150	61.116	56.104	-7.566	1.00	17.26	A	C
ATOM	1188	O	PHE	A	150	60.229	55.324	-7.235	1.00	17.41	A	O
ATOM	1189	CB	PHE	A	150	62.054	57.925	-6.045	1.00	16.20	A	C
ATOM	1190	CG	PHE	A	150	61.904	57.072	-4.808	1.00	15.43	A	C
ATOM	1191	CD1	PHE	A	150	61.042	57.450	-3.805	1.00	18.11	A	C
ATOM	1192	CD2	PHE	A	150	62.614	55.885	-4.681	1.00	17.12	A	C
ATOM	1193	CE1	PHE	A	150	60.883	56.655	-2.694	1.00	16.60	A	C
ATOM	1194	CE2	PHE	A	150	62.477	55.092	-3.564	1.00	16.66	A	C
ATOM	1195	CZ	PHE	A	150	61.588	55.468	-2.576	1.00	18.98	A	C
ATOM	1196	N	SER	A	151	62.143	55.741	-8.320	1.00	15.58	A	N
ATOM	1197	CA	SER	A	151	62.353	54.360	-8.764	1.00	13.42	A	C
ATOM	1198	C	SER	A	151	63.779	53.904	-8.612	1.00	15.43	A	C
ATOM	1199	O	SER	A	151	64.717	54.708	-8.638	1.00	17.96	A	O
ATOM	1200	CB	SER	A	151	61.880	54.171	-10.200	1.00	18.86	A	C
ATOM	1201	OG	SER	A	151	62.440	55.169	-11.021	1.00	19.88	A	O
ATOM	1202	N	LEU	A	152	63.932	52.603	-8.401	1.00	15.64	A	N
ATOM	1203	CA	LEU	A	152	65.213	51.992	-8.105	1.00	16.25	A	C
ATOM	1204	C	LEU	A	152	65.456	50.817	-9.015	1.00	17.29	A	C
ATOM	1205	O	LEU	A	152	64.596	49.925	-9.143	1.00	17.99	A	O
ATOM	1206	CB	LEU	A	152	65.248	51.493	-6.650	1.00	16.35	A	C
ATOM	1207	CG	LEU	A	152	65.317	52.590	-5.590	1.00	18.65	A	C
ATOM	1208	CD1	LEU	A	152	65.177	51.994	-4.208	1.00	19.71	A	C
ATOM	1209	CD2	LEU	A	152	66.585	53.418	-5.725	1.00	19.60	A	C
ATOM	1210	N	GLN	A	153	66.618	50.820	-9.646	1.00	19.70	A	N
ATOM	1211	CA	GLN	A	153	67.115	49.692	-10.419	1.00	19.09	A	C
ATOM	1212	C	GLN	A	153	68.422	49.296	-9.747	1.00	17.61	A	C
ATOM	1213	O	GLN	A	153	69.438	49.964	-9.921	1.00	22.26	A	O
ATOM	1214	CB	GLN	A	153	67.368	50.078	-11.883	1.00	23.44	A	C
ATOM	1215	CG	GLN	A	153	67.771	48.873	-12.721	1.00	24.58	A	C
ATOM	1216	CD	GLN	A	153	68.573	49.194	-13.957	1.00	26.89	A	C
ATOM	1217	OE1	GLN	A	153	69.610	49.863	-13.895	1.00	32.38	A	O
ATOM	1218	NE2	GLN	A	153	68.116	48.681	-15.089	1.00	27.76	A	N
ATOM	1219	N	LEU	A	154	68.392	48.247	-8.941	1.00	17.74	A	N
ATOM	1220	CA	LEU	A	154	69.618	47.726	-8.329	1.00	21.30	A	C
ATOM	1221	C	LEU	A	154	70.186	46.576	-9.166	1.00	28.90	A	C
ATOM	1222	O	LEU	A	154	69.479	45.609	-9.464	1.00	29.97	A	O
ATOM	1223	CB	LEU	A	154	69.339	47.276	-6.898	1.00	21.73	A	C
ATOM	1224	CG	LEU	A	154	68.556	48.277	-6.046	1.00	22.21	A	C
ATOM	1225	CD1	LEU	A	154	68.239	47.712	-4.686	1.00	25.89	A	C
ATOM	1226	CD2	LEU	A	154	69.266	49.619	-5.888	1.00	22.60	A	C
ATOM	1227	N	CYS	A	155	71.461	46.678	-9.537	1.00	32.67	A	N
ATOM	1228	CA	CYS	A	155	72.096	45.709	-10.442	1.00	36.54	A	C
ATOM	1229	C	CYS	A	155	73.103	44.805	-9.720	1.00	41.47	A	C

ATOM	1230	O	CYS	A	155	72.719	43.815	-9.116	1.00	43.64	A	O
ATOM	1231	CB	CYS	A	155	72.744	46.440	-11.616	1.00	36.93	A	C
ATOM	1232	SG	CYS	A	155	71.580	47.462	-12.528	1.00	37.02	A	S
ATOM	1233	N	GLY	A	156	74.389	45.122	-9.802	1.00	49.66	A	N
ATOM	1234	CA	GLY	A	156	75.416	44.312	-9.170	1.00	52.13	A	C
ATOM	1235	C	GLY	A	156	75.784	43.035	-9.897	1.00	54.64	A	C
ATOM	1236	O	GLY	A	156	75.586	41.937	-9.372	1.00	55.03	A	O
ATOM	1237	N	ALA	A	157	76.323	43.196	-11.106	1.00	58.96	A	N
ATOM	1238	CA	ALA	A	157	76.935	42.104	-11.872	1.00	59.70	A	C
ATOM	1239	C	ALA	A	157	76.142	40.799	-11.808	1.00	61.26	A	C
ATOM	1240	O	ALA	A	157	76.543	39.845	-11.131	1.00	63.37	A	O
ATOM	1241	CB	ALA	A	157	78.377	41.881	-11.396	1.00	61.07	A	C
ATOM	1242	N	ALA	A	168	81.887	41.703	-5.577	1.00	52.10	A	N
ATOM	1243	CA	ALA	A	168	82.673	42.857	-6.011	1.00	51.66	A	C
ATOM	1244	C	ALA	A	168	81.807	44.132	-6.026	1.00	49.66	A	C
ATOM	1245	O	ALA	A	168	80.833	44.234	-5.270	1.00	47.62	A	O
ATOM	1246	CB	ALA	A	168	83.302	42.585	-7.389	1.00	52.14	A	C
ATOM	1247	N	SER	A	169	82.169	45.100	-6.865	1.00	48.50	A	N
ATOM	1248	CA	SER	A	169	81.455	46.373	-6.933	1.00	47.11	A	C
ATOM	1249	C	SER	A	169	80.128	46.241	-7.693	1.00	45.49	A	C
ATOM	1250	O	SER	A	169	80.102	45.793	-8.833	1.00	42.21	A	O
ATOM	1251	CB	SER	A	169	82.336	47.432	-7.596	1.00	48.06	A	C
ATOM	1252	OG	SER	A	169	81.625	48.637	-7.812	1.00	53.03	A	O
ATOM	1253	N	VAL	A	170	79.036	46.648	-7.048	1.00	40.36	A	N
ATOM	1254	CA	VAL	A	170	77.714	46.662	-7.675	1.00	36.88	A	C
ATOM	1255	C	VAL	A	170	77.329	48.074	-8.121	1.00	33.45	A	C
ATOM	1256	O	VAL	A	170	77.980	49.050	-7.751	1.00	27.09	A	O
ATOM	1257	CB	VAL	A	170	76.636	46.100	-6.714	1.00	35.68	A	C
ATOM	1258	CG1	VAL	A	170	76.978	44.662	-6.301	1.00	38.27	A	C
ATOM	1259	CG2	VAL	A	170	76.471	46.986	-5.476	1.00	36.83	A	C
ATOM	1260	N	GLY	A	171	76.256	48.174	-8.905	1.00	30.02	A	N
ATOM	1261	CA	GLY	A	171	75.760	49.457	-9.360	1.00	28.27	A	C
ATOM	1262	C	GLY	A	171	74.250	49.511	-9.521	1.00	23.99	A	C
ATOM	1263	O	GLY	A	171	73.567	48.502	-9.456	1.00	30.07	A	O
ATOM	1264	N	GLY	A	172	73.748	50.704	-9.785	1.00	22.93	A	N
ATOM	1265	CA	GLY	A	172	72.321	50.912	-9.960	1.00	24.79	A	C
ATOM	1266	C	GLY	A	172	71.921	52.328	-10.318	1.00	21.72	A	C
ATOM	1267	O	GLY	A	172	72.755	53.177	-10.586	1.00	20.97	A	O
ATOM	1268	N	SER	A	173	70.615	52.576	-10.323	1.00	20.55	A	N
ATOM	1269	CA	SER	A	173	70.056	53.881	-10.618	1.00	19.75	A	C
ATOM	1270	C	SER	A	173	68.934	54.169	-9.642	1.00	17.92	A	C
ATOM	1271	O	SER	A	173	68.098	53.318	-9.396	1.00	19.13	A	O
ATOM	1272	CB	SER	A	173	69.490	53.959	-12.045	1.00	20.34	A	C
ATOM	1273	OG	SER	A	173	70.498	53.718	-13.025	1.00	23.31	A	O
ATOM	1274	N	MET	A	174	68.935	55.371	-9.085	1.00	19.22	A	N
ATOM	1275	CA	MET	A	174	67.794	55.904	-8.368	1.00	19.42	A	C
ATOM	1276	C	MET	A	174	67.284	57.099	-9.164	1.00	20.07	A	C
ATOM	1277	O	MET	A	174	67.936	58.150	-9.226	1.00	18.63	A	O
ATOM	1278	CB	MET	A	174	68.156	56.332	-6.953	1.00	19.01	A	C
ATOM	1279	CG	MET	A	174	66.982	56.914	-6.230	1.00	22.45	A	C
ATOM	1280	SD	MET	A	174	67.349	57.388	-4.532	1.00	24.52	A	S
ATOM	1281	CE	MET	A	174	68.659	58.440	-4.766	1.00	27.89	A	C
ATOM	1282	N	ILE	A	175	66.135	56.904	-9.818	1.00	21.08	A	N
ATOM	1283	CA	ILE	A	175	65.469	57.972	-10.548	1.00	16.99	A	C
ATOM	1284	C	ILE	A	175	64.484	58.690	-9.642	1.00	16.84	A	C
ATOM	1285	O	ILE	A	175	63.468	58.119	-9.242	1.00	19.54	A	O
ATOM	1286	CB	ILE	A	175	64.740	57.415	-11.800	1.00	22.71	A	C
ATOM	1287	CG1	ILE	A	175	65.645	56.492	-12.632	1.00	21.64	A	C
ATOM	1288	CG2	ILE	A	175	64.160	58.559	-12.633	1.00	22.47	A	C
ATOM	1289	CD1	ILE	A	175	66.942	57.124	-13.192	1.00	21.34	A	C
ATOM	1290	N	ILE	A	176	64.820	59.929	-9.276	1.00	22.11	A	N
ATOM	1291	CA	ILE	A	176	64.012	60.750	-8.396	1.00	22.51	A	C
ATOM	1292	C	ILE	A	176	63.045	61.581	-9.230	1.00	23.28	A	C
ATOM	1293	O	ILE	A	176	63.464	62.397	-10.056	1.00	27.99	A	O
ATOM	1294	CB	ILE	A	176	64.908	61.703	-7.567	1.00	24.59	A	C
ATOM	1295	CG1	ILE	A	176	65.914	60.917	-6.718	1.00	27.72	A	C
ATOM	1296	CG2	ILE	A	176	64.059	62.601	-6.699	1.00	26.83	A	C
ATOM	1297	CD1	ILE	A	176	65.274	60.104	-5.618	1.00	30.97	A	C
ATOM	1298	N	GLY	A	177	61.762	61.359	-9.003	1.00	23.04	A	N
ATOM	1299	CA	GLY	A	177	60.711	62.169	-9.578	1.00	23.58	A	C
ATOM	1300	C	GLY	A	177	60.114	61.540	-10.810	1.00	27.69	A	C
ATOM	1301	O	GLY	A	177	59.224	62.125	-11.428	1.00	29.57	A	O
ATOM	1302	N	GLY	A	178	60.561	60.340	-11.160	1.00	24.14	A	N
ATOM	1303	CA	GLY	A	178	60.023	59.706	-12.342	1.00	26.72	A	C
ATOM	1304	C	GLY	A	178	60.460	58.295	-12.586	1.00	27.37	A	C
ATOM	1305	O	GLY	A	178	61.017	57.610	-11.712	1.00	24.67	A	O
ATOM	1306	N	ILE	A	179	60.153	57.861	-13.800	1.00	24.35	A	N

ATOM	1307	CA	ILE	A	179	60.475	56.541	-14.300	1.00	28.10	A	C
ATOM	1308	C	ILE	A	179	61.277	56.703	-15.591	1.00	30.00	A	C
ATOM	1309	O	ILE	A	179	61.031	57.640	-16.367	1.00	29.66	A	O
ATOM	1310	CB	ILE	A	179	59.174	55.751	-14.552	1.00	28.71	A	C
ATOM	1311	CG1	ILE	A	179	58.240	55.833	-13.314	1.00	31.09	A	C
ATOM	1312	CG2	ILE	A	179	59.480	54.319	-14.890	1.00	32.54	A	C
ATOM	1313	CD1	ILE	A	179	56.941	55.086	-13.456	1.00	35.50	A	C
ATOM	1314	N	ASP	A	180	62.241	55.806	-15.795	1.00	29.78	A	N
ATOM	1315	CA	ASP	A	180	63.094	55.783	-16.983	1.00	32.20	A	C
ATOM	1316	C	ASP	A	180	62.895	54.450	-17.703	1.00	30.45	A	C
ATOM	1317	O	ASP	A	180	63.345	53.399	-17.240	1.00	27.79	A	O
ATOM	1318	CB	ASP	A	180	64.566	55.955	-16.576	1.00	31.37	A	C
ATOM	1319	CG	ASP	A	180	65.488	56.151	-17.759	1.00	37.38	A	C
ATOM	1320	OD1	ASP	A	180	65.155	55.692	-18.868	1.00	40.09	A	O
ATOM	1321	OD2	ASP	A	180	66.577	56.746	-17.670	1.00	37.04	A	O
ATOM	1322	N	HIS	A	181	62.235	54.504	-18.856	1.00	34.60	A	N
ATOM	1323	CA	HIS	A	181	61.829	53.298	-19.592	1.00	34.97	A	C
ATOM	1324	C	HIS	A	181	62.986	52.434	-20.108	1.00	35.24	A	C
ATOM	1325	O	HIS	A	181	62.825	51.229	-20.323	1.00	34.58	A	O
ATOM	1326	CB	HIS	A	181	60.868	53.695	-20.721	1.00	38.80	A	C
ATOM	1327	CG	HIS	A	181	59.662	54.442	-20.233	0.50	38.66	A	C
ATOM	1328	ND1	HIS	A	181	58.846	53.959	-19.234	0.50	38.35	A	N
ATOM	1329	CD2	HIS	A	181	59.158	55.649	-20.580	0.50	40.41	A	C
ATOM	1330	CE1	HIS	A	181	57.880	54.828	-18.998	0.50	40.15	A	C
ATOM	1331	NE2	HIS	A	181	58.045	55.863	-19.803	0.50	40.15	A	N
ATOM	1332	N	SER	A	182	64.167	53.026	-20.244	1.00	33.98	A	N
ATOM	1333	CA	SER	A	182	65.369	52.269	-20.589	1.00	34.19	A	C
ATOM	1334	C	SER	A	182	65.834	51.304	-19.484	1.00	31.16	A	C
ATOM	1335	O	SER	A	182	66.638	50.418	-19.736	1.00	29.95	A	O
ATOM	1336	CB	SER	A	182	66.507	53.230	-20.966	1.00	36.56	A	C
ATOM	1337	OG	SER	A	182	66.853	54.088	-19.886	1.00	39.80	A	O
ATOM	1338	N	LEU	A	183	65.318	51.458	-18.261	1.00	28.19	A	N
ATOM	1339	CA	LEU	A	183	65.719	50.607	-17.156	1.00	26.88	A	C
ATOM	1340	C	LEU	A	183	64.920	49.310	-17.012	1.00	26.28	A	C
ATOM	1341	O	LEU	A	183	65.267	48.479	-16.178	1.00	21.62	A	O
ATOM	1342	CB	LEU	A	183	65.646	51.397	-15.838	1.00	26.71	A	C
ATOM	1343	CG	LEU	A	183	66.557	52.620	-15.805	1.00	30.09	A	C
ATOM	1344	CD1	LEU	A	183	66.413	53.360	-14.479	1.00	28.34	A	C
ATOM	1345	CD2	LEU	A	183	67.997	52.185	-16.027	1.00	33.43	A	C
ATOM	1346	N	TYR	A	184	63.865	49.130	-17.822	1.00	26.39	A	N
ATOM	1347	CA	TYR	A	184	63.038	47.935	-17.710	1.00	22.78	A	C
ATOM	1348	C	TYR	A	184	62.486	47.453	-19.040	1.00	22.69	A	C
ATOM	1349	O	TYR	A	184	62.380	48.227	-19.990	1.00	23.92	A	O
ATOM	1350	CB	TYR	A	184	61.856	48.135	-16.742	1.00	22.73	A	C
ATOM	1351	CG	TYR	A	184	60.726	49.040	-17.193	1.00	20.79	A	C
ATOM	1352	CD1	TYR	A	184	59.540	48.523	-17.735	1.00	21.72	A	C
ATOM	1353	CD2	TYR	A	184	60.812	50.410	-17.035	1.00	23.49	A	C
ATOM	1354	CE1	TYR	A	184	58.500	49.357	-18.123	1.00	23.85	A	C
ATOM	1355	CE2	TYR	A	184	59.776	51.250	-17.395	1.00	21.72	A	C
ATOM	1356	CZ	TYR	A	184	58.616	50.718	-17.949	1.00	23.96	A	C
ATOM	1357	OH	TYR	A	184	57.603	51.567	-18.306	1.00	27.89	A	O
ATOM	1358	N	THR	A	185	62.082	46.190	-19.048	1.00	26.60	A	N
ATOM	1359	CA	THR	A	185	61.397	45.590	-20.194	1.00	23.12	A	C
ATOM	1360	C	THR	A	185	60.012	45.120	-19.777	1.00	26.64	A	C
ATOM	1361	O	THR	A	185	59.754	44.849	-18.608	1.00	24.65	A	O
ATOM	1362	CB	THR	A	185	62.215	44.414	-20.801	1.00	25.79	A	C
ATOM	1363	OG1	THR	A	185	62.261	43.299	-19.906	1.00	28.94	A	O
ATOM	1364	CG2	THR	A	185	63.702	44.791	-20.980	1.00	32.36	A	C
ATOM	1365	N	GLY	A	186	59.127	44.998	-20.762	1.00	30.22	A	N
ATOM	1366	CA	GLY	A	186	57.765	44.602	-20.489	1.00	28.03	A	C
ATOM	1367	C	GLY	A	186	57.019	45.726	-19.805	1.00	24.17	A	C
ATOM	1368	O	GLY	A	186	57.380	46.894	-19.927	1.00	29.37	A	O
ATOM	1369	N	SER	A	187	55.952	45.365	-19.102	1.00	23.81	A	N
ATOM	1370	CA	SER	A	187	55.062	46.328	-18.488	1.00	21.71	A	C
ATOM	1371	C	SER	A	187	55.311	46.342	-16.996	1.00	19.66	A	C
ATOM	1372	O	SER	A	187	55.732	45.342	-16.426	1.00	20.42	A	O
ATOM	1373	CB	SER	A	187	53.601	45.940	-18.750	1.00	23.20	A	C
ATOM	1374	OG	SER	A	187	52.695	46.740	-18.000	1.00	25.16	A	O
ATOM	1375	N	LEU	A	188	55.046	47.493	-16.390	1.00	18.89	A	N
ATOM	1376	CA	LEU	A	188	54.965	47.608	-14.928	1.00	17.77	A	C
ATOM	1377	C	LEU	A	188	53.629	47.054	-14.466	1.00	19.39	A	C
ATOM	1378	O	LEU	A	188	52.601	47.299	-15.082	1.00	21.63	A	O
ATOM	1379	CB	LEU	A	188	55.067	49.054	-14.470	1.00	18.74	A	C
ATOM	1380	CG	LEU	A	188	56.433	49.736	-14.522	1.00	18.45	A	C
ATOM	1381	CD1	LEU	A	188	56.311	51.222	-14.556	1.00	20.69	A	C
ATOM	1382	CD2	LEU	A	188	57.295	49.273	-13.305	1.00	19.48	A	C
ATOM	1383	N	TRP	A	189	53.670	46.295	-13.384	1.00	13.99	A	N

ATOM	1384	CA	TRP	A	189	52.524	45.838	-12.633	1.00	15.66	A	C
ATOM	1385	C	TRP	A	189	52.595	46.453	-11.245	1.00	16.26	A	C
ATOM	1386	O	TRP	A	189	53.650	46.442	-10.633	1.00	17.41	A	O
ATOM	1387	CB	TRP	A	189	52.542	44.325	-12.516	1.00	15.88	A	C
ATOM	1388	CG	TRP	A	189	52.121	43.681	-13.817	1.00	18.59	A	C
ATOM	1389	CD1	TRP	A	189	52.916	43.461	-14.898	1.00	21.85	A	C
ATOM	1390	CD2	TRP	A	189	50.800	43.262	-14.200	1.00	18.24	A	C
ATOM	1391	NE1	TRP	A	189	52.189	42.888	-15.919	1.00	23.05	A	N
ATOM	1392	CE2	TRP	A	189	50.885	42.772	-15.522	1.00	19.78	A	C
ATOM	1393	CE3	TRP	A	189	49.552	43.264	-13.570	1.00	15.96	A	C
ATOM	1394	CZ2	TRP	A	189	49.777	42.292	-16.224	1.00	20.18	A	C
ATOM	1395	CZ3	TRP	A	189	48.436	42.778	-14.274	1.00	17.80	A	C
ATOM	1396	CH2	TRP	A	189	48.570	42.298	-15.590	1.00	16.72	A	C
ATOM	1397	N	TYR	A	190	51.467	46.920	-10.739	1.00	14.59	A	N
ATOM	1398	CA	TYR	A	190	51.425	47.625	-9.453	1.00	14.85	A	C
ATOM	1399	C	TYR	A	190	50.631	46.901	-8.353	1.00	17.95	A	C
ATOM	1400	O	TYR	A	190	49.564	46.289	-8.586	1.00	13.30	A	O
ATOM	1401	CB	TYR	A	190	50.864	49.021	-9.636	1.00	13.88	A	C
ATOM	1402	CG	TYR	A	190	51.635	49.973	-10.515	1.00	15.59	A	C
ATOM	1403	CD1	TYR	A	190	52.573	50.842	-9.977	1.00	15.38	A	C
ATOM	1404	CD2	TYR	A	190	51.339	50.092	-11.866	1.00	17.42	A	C
ATOM	1405	CE1	TYR	A	190	53.237	51.770	-10.760	1.00	17.56	A	C
ATOM	1406	CE2	TYR	A	190	52.018	51.038	-12.685	1.00	14.93	A	C
ATOM	1407	CZ	TYR	A	190	52.954	51.873	-12.107	1.00	18.74	A	C
ATOM	1408	OH	TYR	A	190	53.638	52.785	-12.865	1.00	17.23	A	O
ATOM	1409	N	THR	A	191	51.182	46.980	-7.139	1.00	16.74	A	N
ATOM	1410	CA	THR	A	191	50.568	46.429	-5.953	1.00	15.64	A	C
ATOM	1411	C	THR	A	191	50.304	47.626	-5.008	1.00	17.89	A	C
ATOM	1412	O	THR	A	191	51.106	48.544	-4.975	1.00	16.52	A	O
ATOM	1413	CB	THR	A	191	51.520	45.392	-5.357	1.00	16.95	A	C
ATOM	1414	OG1	THR	A	191	50.861	44.672	-4.325	1.00	19.32	A	O
ATOM	1415	CG2	THR	A	191	52.768	46.057	-4.680	1.00	16.37	A	C
ATOM	1416	N	PRO	A	192	49.168	47.686	-4.309	1.00	20.12	A	N
ATOM	1417	CA	PRO	A	192	48.944	48.801	-3.365	1.00	21.23	A	C
ATOM	1418	C	PRO	A	192	49.911	48.871	-2.178	1.00	17.60	A	C
ATOM	1419	O	PRO	A	192	50.370	47.856	-1.643	1.00	24.36	A	O
ATOM	1420	CB	PRO	A	192	47.504	48.585	-2.876	1.00	21.11	A	C
ATOM	1421	CG	PRO	A	192	46.881	47.748	-3.955	1.00	22.26	A	C
ATOM	1422	CD	PRO	A	192	47.980	46.828	-4.424	1.00	23.51	A	C
ATOM	1423	N	ILE	A	193	50.235	50.099	-1.797	1.00	21.72	A	N
ATOM	1424	CA	ILE	A	193	50.881	50.339	-0.515	1.00	22.71	A	C
ATOM	1425	C	ILE	A	193	49.758	50.230	0.508	1.00	23.63	A	C
ATOM	1426	O	ILE	A	193	48.881	51.079	0.568	1.00	29.68	A	O
ATOM	1427	CB	ILE	A	193	51.550	51.713	-0.453	1.00	24.36	A	C
ATOM	1428	CG1	ILE	A	193	52.730	51.781	-1.438	1.00	24.14	A	C
ATOM	1429	CG2	ILE	A	193	52.036	51.993	0.987	1.00	24.12	A	C
ATOM	1430	CD1	ILE	A	193	53.313	53.171	-1.629	1.00	22.49	A	C
ATOM	1431	N	ARG	A	194	49.764	49.145	1.257	1.00	29.07	A	N
ATOM	1432	CA	ARG	A	194	48.696	48.887	2.199	1.00	32.57	A	C
ATOM	1433	C	ARG	A	194	48.547	50.005	3.219	1.00	33.92	A	C
ATOM	1434	O	ARG	A	194	47.446	50.517	3.435	1.00	36.50	A	O
ATOM	1435	CB	ARG	A	194	48.940	47.592	2.930	1.00	31.65	A	C
ATOM	1436	CG	ARG	A	194	47.768	47.245	3.797	1.00	32.32	A	C
ATOM	1437	CD	ARG	A	194	48.031	46.137	4.719	1.00	34.05	A	C
ATOM	1438	NE	ARG	A	194	46.832	45.833	5.482	1.00	37.69	A	N
ATOM	1439	CZ	ARG	A	194	46.774	44.914	6.424	1.00	43.49	A	C
ATOM	1440	NH1	ARG	A	194	47.853	44.211	6.726	1.00	45.66	A	N
ATOM	1441	NH2	ARG	A	194	45.636	44.700	7.079	1.00	44.35	A	N
ATOM	1442	N	ARG	A	195	49.668	50.353	3.839	1.00	35.28	A	N
ATOM	1443	CA	ARG	A	195	49.740	51.436	4.817	1.00	35.11	A	C
ATOM	1444	C	ARG	A	195	51.059	52.190	4.631	1.00	32.34	A	C
ATOM	1445	O	ARG	A	195	52.089	51.576	4.401	1.00	28.84	A	O
ATOM	1446	CB	ARG	A	195	49.683	50.857	6.226	1.00	35.59	A	C
ATOM	1447	CG	ARG	A	195	49.645	51.910	7.339	1.00	40.30	A	C
ATOM	1448	CD	ARG	A	195	48.907	51.460	8.591	1.00	43.51	A	C
ATOM	1449	NE	ARG	A	195	49.734	50.619	9.458	1.00	44.69	A	N
ATOM	1450	CZ	ARG	A	195	50.582	51.069	10.387	1.00	46.19	A	C
ATOM	1451	NH1	ARG	A	195	50.753	52.371	10.585	1.00	46.87	A	N
ATOM	1452	NH2	ARG	A	195	51.274	50.201	11.124	1.00	46.12	A	N
ATOM	1453	N	GLU	A	196	51.016	53.508	4.766	1.00	33.16	A	N
ATOM	1454	CA	GLU	A	196	52.167	54.353	4.500	1.00	34.04	A	C
ATOM	1455	C	GLU	A	196	52.963	54.554	5.774	1.00	31.83	A	C
ATOM	1456	O	GLU	A	196	52.790	55.566	6.460	1.00	35.74	A	O
ATOM	1457	CB	GLU	A	196	51.728	55.699	3.953	1.00	33.34	A	C
ATOM	1458	CG	GLU	A	196	50.986	55.643	2.624	1.00	38.79	A	C
ATOM	1459	CD	GLU	A	196	50.230	56.927	2.341	1.00	42.74	A	C
ATOM	1460	OE1	GLU	A	196	49.199	57.182	3.009	1.00	47.60	A	O

ATOM	1461	OE2	GLU	A	196	50.661	57.688	1.450	1.00	42.51	A	O
ATOM	1462	N	TRP	A	197	53.805	53.567	6.075	1.00	29.99	A	N
ATOM	1463	CA	TRP	A	197	54.773	53.629	7.184	1.00	32.01	A	C
ATOM	1464	C	TRP	A	197	56.104	53.059	6.668	1.00	29.04	A	C
ATOM	1465	O	TRP	A	197	56.938	53.829	6.210	1.00	30.54	A	O
ATOM	1466	CB	TRP	A	197	54.229	52.970	8.474	1.00	31.92	A	C
ATOM	1467	CG	TRP	A	197	53.800	51.538	8.412	1.00	36.08	A	C
ATOM	1468	CD1	TRP	A	197	53.091	50.926	7.418	1.00	36.38	A	C
ATOM	1469	CD2	TRP	A	197	54.023	50.532	9.414	1.00	40.65	A	C
ATOM	1470	NE1	TRP	A	197	52.887	49.605	7.726	1.00	40.70	A	N
ATOM	1471	CE2	TRP	A	197	53.446	49.337	8.948	1.00	41.77	A	C
ATOM	1472	CE3	TRP	A	197	54.672	50.518	10.658	1.00	41.22	A	C
ATOM	1473	CZ2	TRP	A	197	53.486	48.146	9.680	1.00	43.13	A	C
ATOM	1474	CZ3	TRP	A	197	54.720	49.337	11.381	1.00	40.93	A	C
ATOM	1475	CH2	TRP	A	197	54.129	48.166	10.891	1.00	42.69	A	C
ATOM	1476	N	TYR	A	198	56.303	51.746	6.699	1.00	24.59	A	N
ATOM	1477	CA	TYR	A	198	57.184	51.077	5.740	1.00	25.69	A	C
ATOM	1478	C	TYR	A	198	56.456	51.094	4.391	1.00	22.71	A	C
ATOM	1479	O	TYR	A	198	55.317	51.519	4.305	1.00	25.15	A	O
ATOM	1480	CB	TYR	A	198	57.455	49.620	6.110	1.00	28.07	A	C
ATOM	1481	CG	TYR	A	198	58.137	49.394	7.453	1.00	32.69	A	C
ATOM	1482	CD1	TYR	A	198	59.514	49.273	7.541	1.00	36.04	A	C
ATOM	1483	CD2	TYR	A	198	57.393	49.289	8.627	1.00	35.45	A	C
ATOM	1484	CE1	TYR	A	198	60.146	49.054	8.769	1.00	35.82	A	C
ATOM	1485	CE2	TYR	A	198	58.015	49.079	9.865	1.00	36.80	A	C
ATOM	1486	CZ	TYR	A	198	59.385	48.962	9.927	1.00	38.75	A	C
ATOM	1487	OH	TYR	A	198	60.007	48.744	11.143	1.00	38.81	A	O
ATOM	1488	N	TYR	A	199	57.142	50.654	3.347	1.00	21.11	A	N
ATOM	1489	CA	TYR	A	199	56.497	50.364	2.048	1.00	21.41	A	C
ATOM	1490	C	TYR	A	199	55.866	48.991	2.152	1.00	18.46	A	C
ATOM	1491	O	TYR	A	199	56.471	47.969	1.784	1.00	18.42	A	O
ATOM	1492	CB	TYR	A	199	57.521	50.484	0.914	1.00	21.15	A	C
ATOM	1493	CG	TYR	A	199	57.861	51.927	0.640	1.00	18.31	A	C
ATOM	1494	CD1	TYR	A	199	56.965	52.770	-0.020	1.00	17.27	A	C
ATOM	1495	CD2	TYR	A	199	59.078	52.478	1.059	1.00	17.06	A	C
ATOM	1496	CE1	TYR	A	199	57.275	54.106	-0.239	1.00	18.14	A	C
ATOM	1497	CE2	TYR	A	199	59.394	53.799	0.816	1.00	14.53	A	C
ATOM	1498	CZ	TYR	A	199	58.510	54.608	0.178	1.00	17.63	A	C
ATOM	1499	OH	TYR	A	199	58.822	55.911	-0.024	1.00	17.71	A	O
ATOM	1500	N	GLU	A	200	54.664	48.979	2.742	1.00	21.57	A	N
ATOM	1501	CA	GLU	A	200	54.004	47.722	3.098	1.00	22.77	A	C
ATOM	1502	C	GLU	A	200	53.206	47.182	1.904	1.00	16.75	A	C
ATOM	1503	O	GLU	A	200	52.457	47.916	1.322	1.00	24.39	A	O
ATOM	1504	CB	GLU	A	200	53.030	47.909	4.260	1.00	24.90	A	C
ATOM	1505	CG	GLU	A	200	52.680	46.604	4.946	1.00	27.85	A	C
ATOM	1506	CD	GLU	A	200	51.514	46.716	5.919	1.00	28.16	A	C
ATOM	1507	OE1	GLU	A	200	51.081	47.840	6.278	1.00	35.16	A	O
ATOM	1508	OE2	GLU	A	200	50.987	45.649	6.300	1.00	34.56	A	O
ATOM	1509	N	VAL	A	201	53.386	45.920	1.596	1.00	22.87	A	N
ATOM	1510	CA	VAL	A	201	52.595	45.240	0.554	1.00	21.15	A	C
ATOM	1511	C	VAL	A	201	52.057	43.892	1.045	1.00	26.77	A	C
ATOM	1512	O	VAL	A	201	52.462	43.402	2.103	1.00	26.68	A	O
ATOM	1513	CB	VAL	A	201	53.455	44.997	-0.684	1.00	22.52	A	C
ATOM	1514	CG1	VAL	A	201	54.012	46.314	-1.198	1.00	22.34	A	C
ATOM	1515	CG2	VAL	A	201	54.593	43.991	-0.400	1.00	23.70	A	C
ATOM	1516	N	ILE	A	202	51.187	43.262	0.248	1.00	20.41	A	N
ATOM	1517	CA	ILE	A	202	50.579	41.984	0.632	1.00	24.08	A	C
ATOM	1518	C	ILE	A	202	50.901	40.908	-0.404	1.00	23.18	A	C
ATOM	1519	O	ILE	A	202	50.569	41.064	-1.572	1.00	21.92	A	O
ATOM	1520	CB	ILE	A	202	49.041	42.119	0.801	1.00	24.91	A	C
ATOM	1521	CG1	ILE	A	202	48.697	43.058	1.967	1.00	28.97	A	C
ATOM	1522	CG2	ILE	A	202	48.410	40.742	1.042	1.00	26.55	A	C
ATOM	1523	CD1	ILE	A	202	47.237	43.384	2.081	1.00	28.35	A	C
ATOM	1524	N	ILE	A	203	51.552	39.836	0.037	1.00	20.58	A	N
ATOM	1525	CA	ILE	A	203	51.806	38.642	-0.749	1.00	23.06	A	C
ATOM	1526	C	ILE	A	203	50.600	37.712	-0.588	1.00	23.74	A	C
ATOM	1527	O	ILE	A	203	50.113	37.480	0.521	1.00	25.10	A	O
ATOM	1528	CB	ILE	A	203	53.097	37.940	-0.293	1.00	24.14	A	C
ATOM	1529	CG1	ILE	A	203	54.310	38.807	-0.656	1.00	25.32	A	C
ATOM	1530	CG2	ILE	A	203	53.196	36.561	-0.924	1.00	23.21	A	C
ATOM	1531	CD1	ILE	A	203	55.655	38.280	-0.193	1.00	30.24	A	C
ATOM	1532	N	VAL	A	204	50.065	37.249	-1.705	1.00	24.79	A	N
ATOM	1533	CA	VAL	A	204	48.827	36.465	-1.685	1.00	22.84	A	C
ATOM	1534	C	VAL	A	204	49.050	34.992	-2.011	1.00	27.15	A	C
ATOM	1535	O	VAL	A	204	48.192	34.158	-1.721	1.00	28.57	A	O
ATOM	1536	CB	VAL	A	204	47.764	37.091	-2.640	1.00	21.80	A	C
ATOM	1537	CG1	VAL	A	204	47.505	38.524	-2.253	1.00	20.60	A	C

ATOM	1538	CG2	VAL	A	204	48.210	36.970	-4.075	1.00	24.51	A	C
ATOM	1539	N	ARG	A	205	50.191	34.678	-2.612	1.00	24.48	A	N
ATOM	1540	CA	ARG	A	205	50.540	33.330	-3.018	1.00	27.35	A	C
ATOM	1541	C	ARG	A	205	52.049	33.204	-3.207	1.00	32.98	A	C
ATOM	1542	O	ARG	A	205	52.755	34.167	-3.563	1.00	24.15	A	O
ATOM	1543	CB	ARG	A	205	49.815	32.977	-4.325	1.00	30.35	A	C
ATOM	1544	CG	ARG	A	205	49.857	31.540	-4.763	1.00	33.44	A	C
ATOM	1545	CD	ARG	A	205	49.122	31.314	-6.095	1.00	36.40	A	C
ATOM	1546	NE	ARG	A	205	49.502	30.060	-6.747	1.00	40.66	A	N
ATOM	1547	CZ	ARG	A	205	48.730	28.978	-6.838	1.00	44.96	A	C
ATOM	1548	NH1	ARG	A	205	47.510	28.961	-6.312	1.00	49.55	A	N
ATOM	1549	NH2	ARG	A	205	49.185	27.893	-7.457	1.00	48.81	A	N
ATOM	1550	N	VAL	A	206	52.548	32.004	-2.961	1.00	31.90	A	N
ATOM	1551	CA	VAL	A	206	53.955	31.713	-3.133	1.00	31.00	A	C
ATOM	1552	C	VAL	A	206	54.077	30.348	-3.747	1.00	36.19	A	C
ATOM	1553	O	VAL	A	206	53.523	29.380	-3.227	1.00	37.64	A	O
ATOM	1554	CB	VAL	A	206	54.727	31.762	-1.786	1.00	34.34	A	C
ATOM	1555	CG1	VAL	A	206	56.208	31.653	-2.026	1.00	38.60	A	C
ATOM	1556	CG2	VAL	A	206	54.407	33.029	-1.020	1.00	34.28	A	C
ATOM	1557	N	GLU	A	207	54.746	30.296	-4.889	1.00	35.57	A	N
ATOM	1558	CA	GLU	A	207	55.129	29.059	-5.525	1.00	40.01	A	C
ATOM	1559	C	GLU	A	207	56.630	28.880	-5.382	1.00	43.14	A	C
ATOM	1560	O	GLU	A	207	57.371	29.858	-5.263	1.00	38.43	A	O
ATOM	1561	CB	GLU	A	207	54.766	29.102	-7.007	1.00	41.74	A	C
ATOM	1562	CG	GLU	A	207	53.270	29.123	-7.274	1.00	41.66	A	C
ATOM	1563	CD	GLU	A	207	52.934	29.348	-8.733	1.00	41.56	A	C
ATOM	1564	OE1	GLU	A	207	53.854	29.540	-9.548	1.00	40.42	A	O
ATOM	1565	OE2	GLU	A	207	51.733	29.347	-9.071	1.00	47.50	A	O
ATOM	1566	N	ILE	A	208	57.063	27.620	-5.371	1.00	44.90	A	N
ATOM	1567	CA	ILE	A	208	58.462	27.260	-5.592	1.00	48.28	A	C
ATOM	1568	C	ILE	A	208	58.488	26.248	-6.737	1.00	50.10	A	C
ATOM	1569	O	ILE	A	208	57.926	25.155	-6.628	1.00	48.21	A	O
ATOM	1570	CB	ILE	A	208	59.106	26.692	-4.312	1.00	48.76	A	C
ATOM	1571	CG1	ILE	A	208	59.185	27.770	-3.227	1.00	50.92	A	C
ATOM	1572	CG2	ILE	A	208	60.499	26.179	-4.607	1.00	50.10	A	C
ATOM	1573	CD1	ILE	A	208	59.221	27.225	-1.835	1.00	52.20	A	C
ATOM	1574	N	ASN	A	209	59.102	26.647	-7.846	1.00	51.40	A	N
ATOM	1575	CA	ASN	A	209	59.111	25.882	-9.091	1.00	56.38	A	C
ATOM	1576	C	ASN	A	209	57.756	25.851	-9.827	1.00	56.68	A	C
ATOM	1577	O	ASN	A	209	57.689	25.425	-10.982	1.00	55.91	A	O
ATOM	1578	CB	ASN	A	209	59.636	24.456	-8.847	1.00	58.04	A	C
ATOM	1579	CG	ASN	A	209	60.332	23.865	-10.064	1.00	60.28	A	C
ATOM	1580	OD1	ASN	A	209	60.251	22.656	-10.316	1.00	65.04	A	O
ATOM	1581	ND2	ASN	A	209	61.025	24.707	-10.820	1.00	62.80	A	N
ATOM	1582	N	GLY	A	210	56.696	26.338	-9.181	1.00	56.56	A	N
ATOM	1583	CA	GLY	A	210	55.345	26.202	-9.699	1.00	56.62	A	C
ATOM	1584	C	GLY	A	210	54.374	25.584	-8.708	1.00	57.30	A	C
ATOM	1585	O	GLY	A	210	53.169	25.564	-8.959	1.00	58.65	A	O
ATOM	1586	N	GLN	A	211	54.885	25.094	-7.582	1.00	56.04	A	N
ATOM	1587	CA	GLN	A	211	54.071	24.409	-6.589	1.00	56.19	A	C
ATOM	1588	C	GLN	A	211	53.873	25.311	-5.383	1.00	55.79	A	C
ATOM	1589	O	GLN	A	211	54.839	25.720	-4.748	1.00	51.74	A	O
ATOM	1590	CB	GLN	A	211	54.761	23.112	-6.168	1.00	58.40	A	C
ATOM	1591	CG	GLN	A	211	54.940	22.113	-7.308	1.00	60.83	A	C
ATOM	1592	CD	GLN	A	211	55.915	20.988	-6.973	1.00	64.24	A	C
ATOM	1593	OE1	GLN	A	211	56.594	20.463	-7.863	1.00	64.43	A	O
ATOM	1594	NE2	GLN	A	211	55.983	20.614	-5.694	1.00	66.64	A	N
ATOM	1595	N	ASP	A	212	52.628	25.626	-5.048	1.00	54.01	A	N
ATOM	1596	CA	ASP	A	212	52.407	26.569	-3.959	1.00	56.91	A	C
ATOM	1597	C	ASP	A	212	52.447	25.914	-2.575	1.00	57.30	A	C
ATOM	1598	O	ASP	A	212	52.369	24.693	-2.454	1.00	55.10	A	O
ATOM	1599	CB	ASP	A	212	51.157	27.428	-4.209	1.00	56.98	A	C
ATOM	1600	CG	ASP	A	212	49.890	26.788	-3.737	1.00	57.67	A	C
ATOM	1601	OD1	ASP	A	212	49.566	25.680	-4.212	1.00	57.46	A	O
ATOM	1602	OD2	ASP	A	212	49.139	27.347	-2.909	1.00	59.70	A	O
ATOM	1603	N	LEU	A	213	52.623	26.738	-1.545	1.00	58.77	A	N
ATOM	1604	CA	LEU	A	213	52.860	26.263	-0.176	1.00	60.89	A	C
ATOM	1605	C	LEU	A	213	51.546	26.024	0.566	1.00	61.05	A	C
ATOM	1606	O	LEU	A	213	51.518	25.356	1.596	1.00	58.81	A	O
ATOM	1607	CB	LEU	A	213	53.725	27.270	0.598	1.00	61.26	A	C
ATOM	1608	CG	LEU	A	213	55.223	27.312	0.263	1.00	62.51	A	C
ATOM	1609	CD1	LEU	A	213	55.490	27.170	-1.234	1.00	62.99	A	C
ATOM	1610	CD2	LEU	A	213	55.857	28.602	0.793	1.00	63.51	A	C
ATOM	1611	N	LYS	A	214	50.470	26.602	0.039	1.00	62.93	A	N
ATOM	1612	CA	LYS	A	214	49.107	26.273	0.441	1.00	65.41	A	C
ATOM	1613	C	LYS	A	214	48.812	26.553	1.915	1.00	64.81	A	C
ATOM	1614	O	LYS	A	214	47.985	25.872	2.523	1.00	66.72	A	O

ATOM	1615	CB	LYS	A	214	48.781	24.808	0.083	1.00	66.77	A	C
ATOM	1616	CG	LYS	A	214	47.364	24.625	-0.469	1.00	69.56	A	C
ATOM	1617	CD	LYS	A	214	46.931	23.158	-0.553	1.00	70.85	A	C
ATOM	1618	CE	LYS	A	214	45.423	23.023	-0.346	1.00	70.83	A	C
ATOM	1619	NZ	LYS	A	214	44.873	21.747	-0.879	1.00	72.20	A	N
ATOM	1620	N	MET	A	215	49.465	27.568	2.480	1.00	62.76	A	N
ATOM	1621	CA	MET	A	215	49.187	27.959	3.862	1.00	61.10	A	C
ATOM	1622	C	MET	A	215	48.402	29.267	3.925	1.00	57.64	A	C
ATOM	1623	O	MET	A	215	48.495	30.102	3.024	1.00	57.95	A	O
ATOM	1624	CB	MET	A	215	50.474	28.035	4.701	1.00	62.37	A	C
ATOM	1625	CG	MET	A	215	51.555	28.957	4.190	1.00	63.11	A	C
ATOM	1626	SD	MET	A	215	53.067	28.833	5.203	1.00	62.67	A	S
ATOM	1627	CE	MET	A	215	54.211	28.376	3.978	1.00	62.72	A	C
ATOM	1628	N	ASP	A	216	47.599	29.420	4.976	1.00	53.34	A	N
ATOM	1629	CA	ASP	A	216	46.873	30.660	5.220	1.00	52.79	A	C
ATOM	1630	C	ASP	A	216	47.755	31.819	4.770	1.00	51.45	A	C
ATOM	1631	O	ASP	A	216	48.861	32.008	5.283	1.00	45.58	A	O
ATOM	1632	CB	ASP	A	216	46.517	30.792	6.705	1.00	53.42	A	C
ATOM	1633	CG	ASP	A	216	45.523	31.911	6.981	1.00	55.05	A	C
ATOM	1634	OD1	ASP	A	216	45.109	32.639	6.045	1.00	53.37	A	O
ATOM	1635	OD2	ASP	A	216	45.096	32.134	8.132	1.00	59.33	A	O
ATOM	1636	N	CYS	A	217	47.285	32.567	3.779	1.00	49.19	A	N
ATOM	1637	CA	CYS	A	217	48.119	33.601	3.172	1.00	49.39	A	C
ATOM	1638	C	CYS	A	217	48.345	34.770	4.144	1.00	48.78	A	C
ATOM	1639	O	CYS	A	217	49.274	35.554	3.966	1.00	49.38	A	O
ATOM	1640	CB	CYS	A	217	47.515	34.072	1.843	1.00	46.23	A	C
ATOM	1641	SG	CYS	A	217	45.917	34.862	2.016	1.00	48.31	A	S
ATOM	1642	N	LYS	A	218	47.489	34.869	5.166	1.00	48.17	A	N
ATOM	1643	CA	LYS	A	218	47.671	35.792	6.291	1.00	46.87	A	C
ATOM	1644	C	LYS	A	218	49.055	35.646	6.937	1.00	44.90	A	C
ATOM	1645	O	LYS	A	218	49.632	36.624	7.446	1.00	37.36	A	O
ATOM	1646	CB	LYS	A	218	46.585	35.551	7.345	1.00	48.51	A	C
ATOM	1647	CG	LYS	A	218	46.222	36.772	8.167	1.00	52.96	A	C
ATOM	1648	CD	LYS	A	218	44.760	36.731	8.616	1.00	54.70	A	C
ATOM	1649	CE	LYS	A	218	44.287	38.081	9.134	1.00	56.36	A	C
ATOM	1650	NZ	LYS	A	218	42.812	38.224	8.965	1.00	58.19	A	N
ATOM	1651	N	GLU	A	219	49.579	34.425	6.899	1.00	41.30	A	N
ATOM	1652	CA	GLU	A	219	50.894	34.118	7.460	1.00	41.57	A	C
ATOM	1653	C	GLU	A	219	52.043	34.739	6.674	1.00	41.40	A	C
ATOM	1654	O	GLU	A	219	53.112	35.003	7.245	1.00	38.39	A	O
ATOM	1655	CB	GLU	A	219	51.129	32.603	7.526	1.00	42.52	A	C
ATOM	1656	CG	GLU	A	219	50.072	31.806	8.284	1.00	43.99	A	C
ATOM	1657	CD	GLU	A	219	50.103	32.015	9.793	1.00	49.15	A	C
ATOM	1658	OE1	GLU	A	219	49.422	31.235	10.503	1.00	49.54	A	O
ATOM	1659	OE2	GLU	A	219	50.786	32.950	10.276	1.00	47.89	A	O
ATOM	1660	N	TYR	A	220	51.851	34.902	5.364	1.00	35.85	A	N
ATOM	1661	CA	TYR	A	220	52.867	35.487	4.479	1.00	35.18	A	C
ATOM	1662	C	TYR	A	220	53.164	36.913	4.830	1.00	28.13	A	C
ATOM	1663	O	TYR	A	220	54.185	37.465	4.445	1.00	34.25	A	O
ATOM	1664	CB	TYR	A	220	52.413	35.452	3.004	1.00	36.98	A	C
ATOM	1665	CG	TYR	A	220	52.256	34.069	2.389	1.00	37.36	A	C
ATOM	1666	CD1	TYR	A	220	51.233	33.809	1.478	1.00	37.78	A	C
ATOM	1667	CD2	TYR	A	220	53.132	33.026	2.702	1.00	40.58	A	C
ATOM	1668	CE1	TYR	A	220	51.093	32.557	0.894	1.00	38.43	A	C
ATOM	1669	CE2	TYR	A	220	52.996	31.775	2.136	1.00	40.55	A	C
ATOM	1670	CZ	TYR	A	220	51.962	31.539	1.233	1.00	41.11	A	C
ATOM	1671	OH	TYR	A	220	51.819	30.299	0.656	1.00	42.27	A	O
ATOM	1672	N	ASN	A	221	52.230	37.542	5.520	1.00	33.23	A	N
ATOM	1673	CA	ASN	A	221	52.322	38.933	5.865	1.00	35.09	A	C
ATOM	1674	C	ASN	A	221	52.201	39.102	7.363	1.00	31.87	A	C
ATOM	1675	O	ASN	A	221	51.682	40.126	7.831	1.00	33.51	A	O
ATOM	1676	CB	ASN	A	221	51.201	39.649	5.143	1.00	36.43	A	C
ATOM	1677	CG	ASN	A	221	51.102	39.213	3.695	1.00	37.85	A	C
ATOM	1678	OD1	ASN	A	221	50.157	38.521	3.300	1.00	33.97	A	O
ATOM	1679	ND2	ASN	A	221	52.119	39.561	2.910	1.00	28.28	A	N
ATOM	1680	N	TYR	A	222	52.668	38.088	8.091	1.00	39.46	A	N
ATOM	1681	CA	TYR	A	222	52.401	37.971	9.525	1.00	42.38	A	C
ATOM	1682	C	TYR	A	222	53.237	39.004	10.244	1.00	43.57	A	C
ATOM	1683	O	TYR	A	222	54.475	38.894	10.348	1.00	33.19	A	O
ATOM	1684	CB	TYR	A	222	52.673	36.559	10.071	1.00	45.87	A	C
ATOM	1685	CG	TYR	A	222	52.591	36.428	11.592	1.00	48.19	A	C
ATOM	1686	CD1	TYR	A	222	51.870	37.337	12.382	1.00	51.26	A	C
ATOM	1687	CD2	TYR	A	222	53.241	35.392	12.236	1.00	51.18	A	C
ATOM	1688	CE1	TYR	A	222	51.815	37.204	13.774	1.00	52.32	A	C
ATOM	1689	CE2	TYR	A	222	53.192	35.245	13.616	1.00	52.66	A	C
ATOM	1690	CZ	TYR	A	222	52.481	36.154	14.381	1.00	54.09	A	C
ATOM	1691	OH	TYR	A	222	52.436	36.004	15.751	1.00	56.15	A	O

ATOM	1692	N	ASP	A	223	52.486	39.968	10.768	1.00	46.73	A	N
ATOM	1693	CA	ASP	A	223	52.934	41.294	11.099	1.00	47.06	A	C
ATOM	1694	C	ASP	A	223	52.865	42.194	9.864	1.00	43.47	A	C
ATOM	1695	O	ASP	A	223	52.008	43.088	9.777	1.00	45.70	A	O
ATOM	1696	CB	ASP	A	223	54.339	41.289	11.693	1.00	50.64	A	C
ATOM	1697	CG	ASP	A	223	54.663	42.585	12.348	1.00	48.82	A	C
ATOM	1698	OD1	ASP	A	223	54.041	42.879	13.392	1.00	56.19	A	O
ATOM	1699	OD2	ASP	A	223	55.483	43.386	11.871	1.00	54.79	A	O
ATOM	1700	N	LYS	A	224	53.745	41.920	8.908	1.00	43.90	A	N
ATOM	1701	CA	LYS	A	224	54.128	42.889	7.872	1.00	43.50	A	C
ATOM	1702	C	LYS	A	224	54.720	42.221	6.651	1.00	38.65	A	C
ATOM	1703	O	LYS	A	224	55.321	41.177	6.749	1.00	37.31	A	O
ATOM	1704	CB	LYS	A	224	55.234	43.791	8.425	1.00	44.84	A	C
ATOM	1705	CG	LYS	A	224	54.814	45.182	8.824	1.00	49.52	A	C
ATOM	1706	CD	LYS	A	224	56.030	46.109	8.874	1.00	50.93	A	C
ATOM	1707	CE	LYS	A	224	56.970	45.783	10.029	1.00	52.43	A	C
ATOM	1708	NZ	LYS	A	224	58.303	45.329	9.550	1.00	53.74	A	N
ATOM	1709	N	SER	A	225	54.605	42.855	5.487	1.00	34.67	A	N
ATOM	1710	CA	SER	A	225	55.428	42.463	4.347	1.00	29.36	A	C
ATOM	1711	C	SER	A	225	55.923	43.766	3.727	1.00	23.18	A	C
ATOM	1712	O	SER	A	225	55.109	44.637	3.491	1.00	24.20	A	O
ATOM	1713	CB	SER	A	225	54.634	41.642	3.319	1.00	33.54	A	C
ATOM	1714	OG	SER	A	225	54.443	40.303	3.737	1.00	31.33	A	O
ATOM	1715	N	ILE	A	226	57.235	43.914	3.514	1.00	24.65	A	N
ATOM	1716	CA	ILE	A	226	57.814	45.209	3.080	1.00	24.70	A	C
ATOM	1717	C	ILE	A	226	58.879	45.132	1.973	1.00	20.50	A	C
ATOM	1718	O	ILE	A	226	59.568	44.138	1.762	1.00	22.18	A	O
ATOM	1719	CB	ILE	A	226	58.378	46.052	4.318	1.00	26.96	A	C
ATOM	1720	CG1	ILE	A	226	59.715	45.495	4.804	1.00	29.94	A	C
ATOM	1721	CG2	ILE	A	226	57.350	46.153	5.417	1.00	29.80	A	C
ATOM	1722	CD1	ILE	A	226	60.392	46.347	5.918	1.00	30.64	A	C
ATOM	1723	N	VAL	A	227	59.046	46.229	1.249	1.00	21.76	A	N
ATOM	1724	CA	VAL	A	227	60.073	46.314	0.221	1.00	20.70	A	C
ATOM	1725	C	VAL	A	227	61.187	47.177	0.820	1.00	22.68	A	C
ATOM	1726	O	VAL	A	227	60.949	48.339	1.114	1.00	25.66	A	O
ATOM	1727	CB	VAL	A	227	59.486	46.982	-1.036	1.00	22.09	A	C
ATOM	1728	CG1	VAL	A	227	60.466	46.919	-2.217	1.00	22.41	A	C
ATOM	1729	CG2	VAL	A	227	58.172	46.322	-1.385	1.00	22.10	A	C
ATOM	1730	N	ASP	A	228	62.377	46.598	1.025	1.00	25.94	A	N
ATOM	1731	CA	ASP	A	228	63.488	47.250	1.750	1.00	26.69	A	C
ATOM	1732	C	ASP	A	228	64.859	47.181	1.053	1.00	25.68	A	C
ATOM	1733	O	ASP	A	228	65.552	46.160	1.089	1.00	28.14	A	O
ATOM	1734	CB	ASP	A	228	63.610	46.628	3.151	1.00	30.80	A	C
ATOM	1735	CG	ASP	A	228	64.507	47.435	4.073	1.00	36.12	A	C
ATOM	1736	OD1	ASP	A	228	65.240	48.316	3.575	1.00	32.68	A	O
ATOM	1737	OD2	ASP	A	228	64.544	47.261	5.315	1.00	43.13	A	O
ATOM	1738	N	SER	A	229	65.273	48.283	0.448	1.00	20.40	A	N
ATOM	1739	CA	SER	A	229	66.534	48.352	-0.261	1.00	19.83	A	C
ATOM	1740	C	SER	A	229	67.766	48.269	0.668	1.00	20.00	A	C
ATOM	1741	O	SER	A	229	68.848	47.998	0.202	1.00	20.19	A	O
ATOM	1742	CB	SER	A	229	66.608	49.641	-1.084	1.00	19.70	A	C
ATOM	1743	OG	SER	A	229	66.651	50.793	-0.239	1.00	20.04	A	O
ATOM	1744	N	GLY	A	230	67.582	48.539	1.955	1.00	24.02	A	N
ATOM	1745	CA	GLY	A	230	68.666	48.429	2.928	1.00	30.23	A	C
ATOM	1746	C	GLY	A	230	69.016	46.983	3.270	1.00	32.91	A	C
ATOM	1747	O	GLY	A	230	70.179	46.641	3.517	1.00	37.27	A	O
ATOM	1748	N	THR	A	231	67.998	46.129	3.290	1.00	35.70	A	N
ATOM	1749	CA	THR	A	231	68.157	44.736	3.700	1.00	36.19	A	C
ATOM	1750	C	THR	A	231	68.647	43.943	2.502	1.00	36.17	A	C
ATOM	1751	O	THR	A	231	68.125	44.098	1.392	1.00	36.88	A	O
ATOM	1752	CB	THR	A	231	66.811	44.203	4.216	1.00	36.06	A	C
ATOM	1753	OG1	THR	A	231	66.371	44.988	5.333	1.00	41.33	A	O
ATOM	1754	CG2	THR	A	231	66.931	42.806	4.770	1.00	39.41	A	C
ATOM	1755	N	THR	A	232	69.676	43.117	2.701	1.00	34.96	A	N
ATOM	1756	CA	THR	A	232	70.213	42.299	1.624	1.00	31.73	A	C
ATOM	1757	C	THR	A	232	69.299	41.111	1.311	1.00	35.19	A	C
ATOM	1758	O	THR	A	232	69.149	40.754	0.150	1.00	34.98	A	O
ATOM	1759	CB	THR	A	232	71.612	41.737	1.968	1.00	36.41	A	C
ATOM	1760	OG1	THR	A	232	72.502	42.796	2.338	1.00	33.05	A	O
ATOM	1761	CG2	THR	A	232	72.274	41.136	0.735	1.00	36.22	A	C
ATOM	1762	N	ASN	A	233	68.735	40.502	2.352	1.00	38.19	A	N
ATOM	1763	CA	ASN	A	233	68.029	39.230	2.211	1.00	41.17	A	C
ATOM	1764	C	ASN	A	233	66.520	39.365	2.052	1.00	40.23	A	C
ATOM	1765	O	ASN	A	233	65.922	40.416	2.327	1.00	39.76	A	O
ATOM	1766	CB	ASN	A	233	68.307	38.323	3.420	1.00	43.40	A	C
ATOM	1767	CG	ASN	A	233	69.767	37.864	3.503	1.00	44.47	A	C
ATOM	1768	OD1	ASN	A	233	70.293	37.678	4.593	1.00	53.39	A	O

ATOM	1769	ND2	ASN	A	233	70.409	37.667	2.360	1.00	47.21	A	N
ATOM	1770	N	LEU	A	234	65.927	38.259	1.613	1.00	39.45	A	N
ATOM	1771	CA	LEU	A	234	64.497	38.025	1.667	1.00	35.83	A	C
ATOM	1772	C	LEU	A	234	64.178	37.466	3.035	1.00	31.21	A	C
ATOM	1773	O	LEU	A	234	64.504	36.342	3.319	1.00	35.53	A	O
ATOM	1774	CB	LEU	A	234	64.119	37.022	0.562	1.00	41.31	A	C
ATOM	1775	CG	LEU	A	234	62.727	36.992	-0.082	1.00	42.04	A	C
ATOM	1776	CD1	LEU	A	234	62.447	35.596	-0.613	1.00	45.40	A	C
ATOM	1777	CD2	LEU	A	234	61.630	37.429	0.851	1.00	42.45	A	C
ATOM	1778	N	ARG	A	235	63.564	38.263	3.906	1.00	39.51	A	N
ATOM	1779	CA	ARG	A	235	63.200	37.811	5.254	1.00	37.00	A	C
ATOM	1780	C	ARG	A	235	61.737	37.315	5.290	1.00	38.00	A	C
ATOM	1781	O	ARG	A	235	60.863	37.918	4.699	1.00	31.41	A	O
ATOM	1782	CB	ARG	A	235	63.434	38.930	6.278	1.00	40.50	A	C
ATOM	1783	CG	ARG	A	235	64.843	39.557	6.210	1.00	43.67	A	C
ATOM	1784	CD	ARG	A	235	65.208	40.478	7.378	1.00	46.74	A	C
ATOM	1785	NE	ARG	A	235	65.177	39.774	8.659	1.00	49.76	A	N
ATOM	1786	CZ	ARG	A	235	64.729	40.272	9.823	1.00	52.94	A	C
ATOM	1787	NH1	ARG	A	235	64.272	41.522	9.918	1.00	51.18	A	N
ATOM	1788	NH2	ARG	A	235	64.743	39.503	10.914	1.00	51.36	A	N
ATOM	1789	N	LEU	A	236	61.473	36.226	6.008	1.00	37.36	A	N
ATOM	1790	CA	LEU	A	236	60.156	35.571	5.992	1.00	37.98	A	C
ATOM	1791	C	LEU	A	236	59.691	35.254	7.408	1.00	39.27	A	C
ATOM	1792	O	LEU	A	236	60.503	34.847	8.230	1.00	37.29	A	O
ATOM	1793	CB	LEU	A	236	60.238	34.271	5.210	1.00	37.66	A	C
ATOM	1794	CG	LEU	A	236	60.689	34.363	3.745	1.00	36.72	A	C
ATOM	1795	CD1	LEU	A	236	60.713	32.994	3.135	1.00	34.34	A	C
ATOM	1796	CD2	LEU	A	236	59.784	35.269	2.922	1.00	37.91	A	C
ATOM	1797	N	PRO	A	237	58.399	35.408	7.719	1.00	37.12	A	N
ATOM	1798	CA	PRO	A	237	57.939	35.039	9.061	1.00	35.72	A	C
ATOM	1799	C	PRO	A	237	58.324	33.600	9.304	1.00	36.04	A	C
ATOM	1800	O	PRO	A	237	58.364	32.870	8.326	1.00	31.43	A	O
ATOM	1801	CB	PRO	A	237	56.425	35.222	8.985	1.00	36.23	A	C
ATOM	1802	CG	PRO	A	237	56.243	36.263	7.917	1.00	36.72	A	C
ATOM	1803	CD	PRO	A	237	57.297	35.918	6.887	1.00	37.44	A	C
ATOM	1804	N	LYS	A	238	58.647	33.213	10.538	1.00	34.49	A	N
ATOM	1805	CA	LYS	A	238	59.098	31.839	10.805	1.00	34.56	A	C
ATOM	1806	C	LYS	A	238	58.322	30.780	10.051	1.00	32.78	A	C
ATOM	1807	O	LYS	A	238	58.908	29.860	9.452	1.00	32.03	A	O
ATOM	1808	CB	LYS	A	238	58.881	31.433	12.243	1.00	34.24	A	C
ATOM	1809	CG	LYS	A	238	59.299	32.363	13.281	1.00	30.75	A	C
ATOM	1810	CD	LYS	A	238	58.868	31.768	14.539	1.00	5.80	A	C
ATOM	1811	CE	LYS	A	238	57.493	31.846	14.975	1.00	27.32	A	C
ATOM	1812	NZ	LYS	A	238	57.007	31.123	16.239	1.00	32.55	A	N
ATOM	1813	N	LYS	A	239	56.998	30.879	10.142	1.00	28.36	A	N
ATOM	1814	CA	LYS	A	239	56.149	29.747	9.735	1.00	37.49	A	C
ATOM	1815	C	LYS	A	239	56.292	29.508	8.233	1.00	35.49	A	C
ATOM	1816	O	LYS	A	239	56.310	28.360	7.762	1.00	30.89	A	O
ATOM	1817	CB	LYS	A	239	54.675	29.990	10.108	1.00	39.29	A	C
ATOM	1818	CG	LYS	A	239	54.110	28.997	11.108	1.00	46.03	A	C
ATOM	1819	CD	LYS	A	239	52.700	29.406	11.566	1.00	48.69	A	C
ATOM	1820	CE	LYS	A	239	51.634	28.404	11.117	1.00	50.81	A	C
ATOM	1821	NZ	LYS	A	239	50.243	28.846	11.463	1.00	49.91	A	N
ATOM	1822	N	VAL	A	240	56.411	30.614	7.497	1.00	32.65	A	N
ATOM	1823	CA	VAL	A	240	56.599	30.569	6.057	1.00	32.95	A	C
ATOM	1824	C	VAL	A	240	58.018	30.172	5.684	1.00	28.03	A	C
ATOM	1825	O	VAL	A	240	58.201	29.484	4.704	1.00	26.73	A	O
ATOM	1826	CB	VAL	A	240	56.323	31.928	5.390	1.00	28.86	A	C
ATOM	1827	CG1	VAL	A	240	56.411	31.801	3.908	1.00	29.02	A	C
ATOM	1828	CG2	VAL	A	240	54.963	32.517	5.818	1.00	33.40	A	C
ATOM	1829	N	PHE	A	241	59.019	30.655	6.430	1.00	31.69	A	N
ATOM	1830	CA	PHE	A	241	60.402	30.267	6.159	1.00	34.11	A	C
ATOM	1831	C	PHE	A	241	60.559	28.745	6.338	1.00	32.98	A	C
ATOM	1832	O	PHE	A	241	61.100	28.029	5.470	1.00	29.40	A	O
ATOM	1833	CB	PHE	A	241	61.360	30.997	7.095	1.00	35.69	A	C
ATOM	1834	CG	PHE	A	241	62.748	30.459	7.057	1.00	39.37	A	C
ATOM	1835	CD1	PHE	A	241	63.601	30.785	6.012	1.00	42.58	A	C
ATOM	1836	CD2	PHE	A	241	63.197	29.583	8.047	1.00	42.39	A	C
ATOM	1837	CE1	PHE	A	241	64.895	30.272	5.968	1.00	43.06	A	C
ATOM	1838	CE2	PHE	A	241	64.479	29.073	8.007	1.00	38.87	A	C
ATOM	1839	CZ	PHE	A	241	65.329	29.419	6.964	1.00	43.23	A	C
ATOM	1840	N	GLU	A	242	60.075	28.249	7.468	1.00	32.78	A	N
ATOM	1841	CA	GLU	A	242	60.011	26.800	7.696	1.00	36.60	A	C
ATOM	1842	C	GLU	A	242	59.505	26.025	6.487	1.00	33.79	A	C
ATOM	1843	O	GLU	A	242	60.160	25.083	6.053	1.00	35.48	A	O
ATOM	1844	CB	GLU	A	242	59.123	26.473	8.899	1.00	37.43	A	C
ATOM	1845	CG	GLU	A	242	59.830	26.686	10.217	1.00	43.87	A	C

ATOM	1846	CD	GLU	A	242	60.878	25.635	10.508	1.00	45.01	A	C
ATOM	1847	OE1	GLU	A	242	61.759	25.906	11.358	1.00	45.07	A	O
ATOM	1848	OE2	GLU	A	242	60.818	24.545	9.888	1.00	52.08	A	O
ATOM	1849	N	ALA	A	243	58.358	26.437	5.942	1.00	34.61	A	N
ATOM	1850	CA	ALA	A	243	57.752	25.723	4.804	1.00	36.67	A	C
ATOM	1851	C	ALA	A	243	58.531	25.984	3.523	1.00	35.54	A	C
ATOM	1852	O	ALA	A	243	58.735	25.093	2.706	1.00	30.69	A	O
ATOM	1853	CB	ALA	A	243	56.307	26.138	4.615	1.00	36.74	A	C
ATOM	1854	N	ALA	A	244	58.961	27.231	3.375	1.00	36.29	A	N
ATOM	1855	CA	ALA	A	244	59.717	27.682	2.224	1.00	36.28	A	C
ATOM	1856	C	ALA	A	244	60.970	26.841	2.063	1.00	36.59	A	C
ATOM	1857	O	ALA	A	244	61.133	26.184	1.058	1.00	35.35	A	O
ATOM	1858	CB	ALA	A	244	60.073	29.142	2.383	1.00	34.54	A	C
ATOM	1859	N	VAL	A	245	61.853	26.884	3.064	1.00	38.90	A	N
ATOM	1860	CA	VAL	A	245	63.002	25.982	3.143	1.00	42.56	A	C
ATOM	1861	C	VAL	A	245	62.658	24.500	2.899	1.00	40.13	A	C
ATOM	1862	O	VAL	A	245	63.341	23.835	2.114	1.00	40.38	A	O
ATOM	1863	CB	VAL	A	245	63.742	26.130	4.515	1.00	43.37	A	C
ATOM	1864	CG1	VAL	A	245	64.651	24.918	4.821	1.00	47.23	A	C
ATOM	1865	CG2	VAL	A	245	64.541	27.420	4.534	1.00	44.13	A	C
ATOM	1866	N	LYS	A	246	61.627	23.974	3.556	1.00	39.54	A	N
ATOM	1867	CA	LYS	A	246	61.270	22.556	3.352	1.00	44.44	A	C
ATOM	1868	C	LYS	A	246	61.172	22.215	1.859	1.00	43.12	A	C
ATOM	1869	O	LYS	A	246	61.745	21.233	1.407	1.00	40.51	A	O
ATOM	1870	CB	LYS	A	246	59.965	22.180	4.068	1.00	46.80	A	C
ATOM	1871	CG	LYS	A	246	59.575	20.695	3.924	1.00	50.38	A	C
ATOM	1872	CD	LYS	A	246	58.263	20.380	4.653	1.00	52.29	A	C
ATOM	1873	CE	LYS	A	246	57.530	19.182	4.042	1.00	54.52	A	C
ATOM	1874	NZ	LYS	A	246	58.452	18.072	3.656	1.00	53.80	A	N
ATOM	1875	N	SER	A	247	60.473	23.051	1.097	1.00	44.68	A	N
ATOM	1876	CA	SER	A	247	60.282	22.809	-0.337	1.00	45.24	A	C
ATOM	1877	C	SER	A	247	61.505	23.062	-1.226	1.00	43.18	A	C
ATOM	1878	O	SER	A	247	61.653	22.423	-2.258	1.00	38.59	A	O
ATOM	1879	CB	SER	A	247	59.126	23.654	-0.869	1.00	45.97	A	C
ATOM	1880	OG	SER	A	247	59.035	23.478	-2.266	1.00	42.87	A	O
ATOM	1881	N	ILE	A	248	62.345	24.027	-0.861	1.00	47.83	A	N
ATOM	1882	CA	ILE	A	248	63.534	24.348	-1.658	1.00	50.81	A	C
ATOM	1883	C	ILE	A	248	64.570	23.241	-1.475	1.00	52.35	A	C
ATOM	1884	O	ILE	A	248	65.200	22.787	-2.440	1.00	48.20	A	O
ATOM	1885	CB	ILE	A	248	64.116	25.716	-1.260	1.00	51.35	A	C
ATOM	1886	CG1	ILE	A	248	63.101	26.823	-1.548	1.00	50.95	A	C
ATOM	1887	CG2	ILE	A	248	65.428	25.983	-2.015	1.00	51.10	A	C
ATOM	1888	CD1	ILE	A	248	63.447	28.154	-0.913	1.00	51.52	A	C
ATOM	1889	N	LYS	A	249	64.725	22.814	-0.227	1.00	53.72	A	N
ATOM	1890	CA	LYS	A	249	65.451	21.585	0.108	1.00	59.31	A	C
ATOM	1891	C	LYS	A	249	65.021	20.377	-0.745	1.00	61.00	A	C
ATOM	1892	O	LYS	A	249	65.871	19.634	-1.233	1.00	58.84	A	O
ATOM	1893	CB	LYS	A	249	65.260	21.257	1.598	1.00	61.17	A	C
ATOM	1894	CG	LYS	A	249	66.419	20.522	2.240	1.00	63.43	A	C
ATOM	1895	CD	LYS	A	249	66.187	20.317	3.740	1.00	65.86	A	C
ATOM	1896	CE	LYS	A	249	66.299	21.620	4.530	1.00	67.19	A	C
ATOM	1897	NZ	LYS	A	249	66.791	21.417	5.929	1.00	68.30	A	N
ATOM	1898	N	ALA	A	250	63.711	20.207	-0.942	1.00	63.51	A	N
ATOM	1899	CA	ALA	A	250	63.160	19.006	-1.589	1.00	66.01	A	C
ATOM	1900	C	ALA	A	250	63.564	18.839	-3.059	1.00	67.43	A	C
ATOM	1901	O	ALA	A	250	64.214	17.861	-3.408	1.00	67.59	A	O
ATOM	1902	CB	ALA	A	250	61.635	18.974	-1.455	1.00	65.47	A	C
ATOM	1903	N	ALA	A	251	63.185	19.783	-3.917	1.00	69.93	A	N
ATOM	1904	CA	ALA	A	251	63.539	19.694	-5.342	1.00	70.60	A	C
ATOM	1905	C	ALA	A	251	64.985	20.123	-5.633	1.00	70.50	A	C
ATOM	1906	O	ALA	A	251	65.364	20.268	-6.794	1.00	69.29	A	O
ATOM	1907	CB	ALA	A	251	62.547	20.488	-6.212	1.00	70.96	A	C
ATOM	1908	N	SER	A	252	65.778	20.338	-4.582	1.00	70.95	A	N
ATOM	1909	CA	SER	A	252	67.213	20.562	-4.718	1.00	72.23	A	C
ATOM	1910	C	SER	A	252	68.016	19.483	-3.985	1.00	73.46	A	C
ATOM	1911	O	SER	A	252	69.189	19.680	-3.661	1.00	71.37	A	O
ATOM	1912	CB	SER	A	252	67.582	21.951	-4.189	1.00	72.68	A	C
ATOM	1913	OG	SER	A	252	67.505	21.999	-2.775	1.00	73.18	A	O
ATOM	1914	N	SER	A	253	67.389	18.332	-3.756	1.00	75.44	A	N
ATOM	1915	CA	SER	A	253	68.011	17.239	-3.011	1.00	77.44	A	C
ATOM	1916	C	SER	A	253	69.079	16.491	-3.819	1.00	79.67	A	C
ATOM	1917	O	SER	A	253	69.783	15.645	-3.263	1.00	79.72	A	O
ATOM	1918	CB	SER	A	253	66.944	16.250	-2.532	1.00	77.46	A	C
ATOM	1919	OG	SER	A	253	66.037	16.870	-1.637	1.00	76.30	A	O
ATOM	1920	N	THR	A	254	69.196	16.799	-5.116	1.00	81.88	A	N
ATOM	1921	CA	THR	A	254	70.232	16.215	-5.983	1.00	83.80	A	C
ATOM	1922	C	THR	A	254	71.624	16.245	-5.334	1.00	85.34	A	C

ATOM	1923	O	THR	A	254	72.423	15.330	-5.538	1.00	85.86	A	O
ATOM	1924	CB	THR	A	254	70.270	16.936	-7.360	1.00	83.52	A	C
ATOM	1925	OG1	THR	A	254	68.992	16.851	-7.999	1.00	83.21	A	O
ATOM	1926	CG2	THR	A	254	71.205	16.228	-8.342	1.00	83.62	A	C
ATOM	1927	N	GLU	A	255	71.909	17.296	-4.565	1.00	86.72	A	N
ATOM	1928	CA	GLU	A	255	73.121	17.354	-3.746	1.00	87.75	A	C
ATOM	1929	C	GLU	A	255	72.785	17.714	-2.302	1.00	88.51	A	C
ATOM	1930	O	GLU	A	255	72.017	18.643	-2.048	1.00	89.05	A	O
ATOM	1931	CB	GLU	A	255	74.103	18.379	-4.307	1.00	87.94	A	C
ATOM	1932	CG	GLU	A	255	74.553	18.101	-5.731	1.00	88.21	A	C
ATOM	1933	CD	GLU	A	255	75.403	19.222	-6.297	1.00	88.85	A	C
ATOM	1934	OE1	GLU	A	255	76.162	19.847	-5.521	1.00	88.18	A	O
ATOM	1935	OE2	GLU	A	255	75.308	19.478	-7.518	1.00	89.16	A	O
ATOM	1936	N	LYS	A	256	73.367	16.973	-1.361	1.00	89.37	A	N
ATOM	1937	CA	LYS	A	256	73.181	17.233	0.066	1.00	89.70	A	C
ATOM	1938	C	LYS	A	256	74.060	18.406	0.515	1.00	89.43	A	C
ATOM	1939	O	LYS	A	256	75.211	18.519	0.090	1.00	90.96	A	O
ATOM	1940	CB	LYS	A	256	73.524	15.976	0.878	1.00	89.79	A	C
ATOM	1941	CG	LYS	A	256	73.344	16.118	2.390	1.00	89.80	A	C
ATOM	1942	CD	LYS	A	256	73.488	14.778	3.106	1.00	89.76	A	C
ATOM	1943	CE	LYS	A	256	74.916	14.250	3.037	1.00	89.66	A	C
ATOM	1944	NZ	LYS	A	256	75.135	13.099	3.955	1.00	89.59	A	N
ATOM	1945	N	PHE	A	257	73.509	19.278	1.359	1.00	88.33	A	N
ATOM	1946	CA	PHE	A	257	74.277	20.358	1.988	1.00	87.80	A	C
ATOM	1947	C	PHE	A	257	73.957	20.434	3.486	1.00	85.90	A	C
ATOM	1948	O	PHE	A	257	72.901	19.963	3.916	1.00	84.62	A	O
ATOM	1949	CB	PHE	A	257	73.977	21.698	1.307	1.00	88.75	A	C
ATOM	1950	CG	PHE	A	257	74.158	21.672	-0.188	1.00	90.18	A	C
ATOM	1951	CD1	PHE	A	257	73.128	22.071	-1.035	1.00	90.73	A	C
ATOM	1952	CD2	PHE	A	257	75.358	21.243	-0.747	1.00	90.65	A	C
ATOM	1953	CE1	PHE	A	257	73.295	22.043	-2.417	1.00	91.50	A	C
ATOM	1954	CE2	PHE	A	257	75.530	21.208	-2.125	1.00	91.35	A	C
ATOM	1955	CZ	PHE	A	257	74.499	21.611	-2.961	1.00	91.69	A	C
ATOM	1956	N	PRO	A	258	74.857	21.019	4.282	1.00	84.41	A	N
ATOM	1957	CA	PRO	A	258	74.671	21.079	5.743	1.00	83.94	A	C
ATOM	1958	C	PRO	A	258	73.334	21.697	6.182	1.00	83.10	A	C
ATOM	1959	O	PRO	A	258	72.764	22.519	5.459	1.00	82.64	A	O
ATOM	1960	CB	PRO	A	258	75.840	21.957	6.218	1.00	83.97	A	C
ATOM	1961	CG	PRO	A	258	76.862	21.878	5.141	1.00	84.54	A	C
ATOM	1962	CD	PRO	A	258	76.116	21.664	3.861	1.00	84.44	A	C
ATOM	1963	N	ASP	A	259	72.852	21.302	7.360	1.00	81.28	A	N
ATOM	1964	CA	ASP	A	259	71.608	21.847	7.916	1.00	79.36	A	C
ATOM	1965	C	ASP	A	259	71.767	23.327	8.300	1.00	76.80	A	C
ATOM	1966	O	ASP	A	259	70.804	24.097	8.228	1.00	75.77	A	O
ATOM	1967	CB	ASP	A	259	71.140	21.025	9.133	1.00	80.43	A	C
ATOM	1968	CG	ASP	A	259	69.749	20.420	8.947	1.00	81.62	A	C
ATOM	1969	OD1	ASP	A	259	69.433	19.944	7.832	1.00	81.91	A	O
ATOM	1970	OD2	ASP	A	259	68.906	20.364	9.870	1.00	82.81	A	O
ATOM	1971	N	GLY	A	260	72.981	23.716	8.694	1.00	72.15	A	N
ATOM	1972	CA	GLY	A	260	73.280	25.095	9.051	1.00	68.23	A	C
ATOM	1973	C	GLY	A	260	73.394	26.055	7.873	1.00	65.01	A	C
ATOM	1974	O	GLY	A	260	73.306	27.266	8.055	1.00	62.06	A	O
ATOM	1975	N	PHE	A	261	73.601	25.529	6.670	1.00	61.00	A	N
ATOM	1976	CA	PHE	A	261	73.582	26.350	5.456	1.00	59.12	A	C
ATOM	1977	C	PHE	A	261	72.247	27.101	5.311	1.00	57.30	A	C
ATOM	1978	O	PHE	A	261	72.217	28.296	5.013	1.00	47.15	A	O
ATOM	1979	CB	PHE	A	261	73.833	25.475	4.222	1.00	59.54	A	C
ATOM	1980	CG	PHE	A	261	73.504	26.148	2.920	1.00	58.56	A	C
ATOM	1981	CD1	PHE	A	261	74.289	27.187	2.447	1.00	57.89	A	C
ATOM	1982	CD2	PHE	A	261	72.415	25.741	2.169	1.00	58.88	A	C
ATOM	1983	CE1	PHE	A	261	73.996	27.807	1.259	1.00	56.77	A	C
ATOM	1984	CE2	PHE	A	261	72.118	26.359	0.972	1.00	58.83	A	C
ATOM	1985	CZ	PHE	A	261	72.912	27.393	0.516	1.00	58.32	A	C
ATOM	1986	N	TRP	A	262	71.151	26.389	5.557	1.00	56.79	A	N
ATOM	1987	CA	TRP	A	262	69.813	26.949	5.396	1.00	58.03	A	C
ATOM	1988	C	TRP	A	262	69.475	27.995	6.467	1.00	58.02	A	C
ATOM	1989	O	TRP	A	262	68.525	28.760	6.296	1.00	57.45	A	O
ATOM	1990	CB	TRP	A	262	68.759	25.832	5.406	1.00	59.10	A	C
ATOM	1991	CG	TRP	A	262	69.026	24.721	4.432	1.00	60.40	A	C
ATOM	1992	CD1	TRP	A	262	69.372	23.430	4.730	1.00	61.96	A	C
ATOM	1993	CD2	TRP	A	262	68.974	24.800	3.003	1.00	61.91	A	C
ATOM	1994	NE1	TRP	A	262	69.535	22.704	3.574	1.00	60.97	A	N
ATOM	1995	CE2	TRP	A	262	69.298	23.520	2.498	1.00	61.58	A	C
ATOM	1996	CE3	TRP	A	262	68.688	25.824	2.092	1.00	62.89	A	C
ATOM	1997	CZ2	TRP	A	262	69.343	23.240	1.132	1.00	62.27	A	C
ATOM	1998	CZ3	TRP	A	262	68.729	25.543	0.731	1.00	63.90	A	C
ATOM	1999	CH2	TRP	A	262	69.057	24.260	0.267	1.00	63.92	A	C

ATOM	2000	N	LEU	A	263	70.236	28.025	7.563	1.00	56.89	A	N
ATOM	2001	CA	LEU	A	263	70.040	29.026	8.626	1.00	57.55	A	C
ATOM	2002	C	LEU	A	263	71.038	30.204	8.576	1.00	55.97	A	C
ATOM	2003	O	LEU	A	263	71.084	31.020	9.501	1.00	51.83	A	O
ATOM	2004	CB	LEU	A	263	70.102	28.355	10.010	1.00	58.30	A	C
ATOM	2005	CG	LEU	A	263	68.913	27.494	10.470	1.00	61.17	A	C
ATOM	2006	CD1	LEU	A	263	67.569	28.209	10.298	1.00	62.02	A	C
ATOM	2007	CD2	LEU	A	263	68.900	26.160	9.759	1.00	61.49	A	C
ATOM	2008	N	GLY	A	264	71.821	30.300	7.501	1.00	54.23	A	N
ATOM	2009	CA	GLY	A	264	72.793	31.378	7.352	1.00	55.51	A	C
ATOM	2010	C	GLY	A	264	73.964	31.272	8.318	1.00	53.62	A	C
ATOM	2011	O	GLY	A	264	74.657	32.259	8.582	1.00	52.01	A	O
ATOM	2012	N	GLU	A	265	74.180	30.057	8.822	1.00	52.02	A	N
ATOM	2013	CA	GLU	A	265	75.202	29.749	9.818	1.00	52.34	A	C
ATOM	2014	C	GLU	A	265	76.498	29.185	9.216	1.00	51.88	A	C
ATOM	2015	O	GLU	A	265	77.521	29.092	9.902	1.00	50.86	A	O
ATOM	2016	CB	GLU	A	265	74.620	28.757	10.823	1.00	53.23	A	C
ATOM	2017	CG	GLU	A	265	73.484	29.351	11.651	1.00	56.42	A	C
ATOM	2018	CD	GLU	A	265	72.811	28.342	12.572	1.00	59.67	A	C
ATOM	2019	OE1	GLU	A	265	73.053	27.121	12.415	1.00	62.41	A	O
ATOM	2020	OE2	GLU	A	265	72.029	28.777	13.451	1.00	58.43	A	O
ATOM	2021	N	GLN	A	266	76.444	28.781	7.951	1.00	48.71	A	N
ATOM	2022	CA	GLN	A	266	77.650	28.438	7.197	1.00	50.93	A	C
ATOM	2023	C	GLN	A	266	77.436	28.743	5.726	1.00	50.91	A	C
ATOM	2024	O	GLN	A	266	76.300	28.790	5.262	1.00	48.81	A	O
ATOM	2025	CB	GLN	A	266	77.919	26.957	7.385	1.00	51.13	A	C
ATOM	2026	CG	GLN	A	266	79.152	26.489	6.603	0.00	20.00	A	C
ATOM	2027	CD	GLN	A	266	79.377	25.016	6.849	0.00	20.00	A	C
ATOM	2028	OE1	GLN	A	266	79.286	24.174	5.970	0.00	20.00	A	O
ATOM	2029	NE2	GLN	A	266	79.677	24.718	8.129	0.00	20.00	A	N
ATOM	2030	N	LEU	A	267	78.523	28.947	4.988	1.00	52.35	A	N
ATOM	2031	CA	LEU	A	267	78.414	29.197	3.555	1.00	55.74	A	C
ATOM	2032	C	LEU	A	267	78.794	27.955	2.759	1.00	55.94	A	C
ATOM	2033	O	LEU	A	267	79.623	27.161	3.189	1.00	55.10	A	O
ATOM	2034	CB	LEU	A	267	79.228	30.427	3.117	1.00	57.95	A	C
ATOM	2035	CG	LEU	A	267	80.592	30.763	3.719	1.00	59.40	A	C
ATOM	2036	CD1	LEU	A	267	81.667	29.797	3.226	1.00	61.73	A	C
ATOM	2037	CD2	LEU	A	267	80.966	32.199	3.379	1.00	59.25	A	C
ATOM	2038	N	VAL	A	268	78.141	27.778	1.614	1.00	59.08	A	N
ATOM	2039	CA	VAL	A	268	78.394	26.635	0.734	1.00	63.27	A	C
ATOM	2040	C	VAL	A	268	79.437	27.028	-0.317	1.00	65.28	A	C
ATOM	2041	O	VAL	A	268	79.581	28.206	-0.628	1.00	65.73	A	O
ATOM	2042	CB	VAL	A	268	77.072	26.103	0.084	1.00	63.60	A	C
ATOM	2043	CG1	VAL	A	268	76.461	27.114	-0.900	1.00	64.14	A	C
ATOM	2044	CG2	VAL	A	268	77.302	24.759	-0.593	1.00	63.65	A	C
ATOM	2045	N	CYS	A	269	80.182	26.050	-0.830	1.00	67.59	A	N
ATOM	2046	CA	CYS	A	269	81.255	26.315	-1.794	1.00	70.85	A	C
ATOM	2047	C	CYS	A	269	81.288	25.302	-2.943	1.00	71.91	A	C
ATOM	2048	O	CYS	A	269	81.068	24.106	-2.740	1.00	70.92	A	O
ATOM	2049	CB	CYS	A	269	82.618	26.330	-1.086	1.00	71.01	A	C
ATOM	2050	SG	CYS	A	269	82.804	27.634	0.160	1.00	73.46	A	S
ATOM	2051	N	TRP	A	270	81.560	25.804	-4.147	1.00	73.59	A	N
ATOM	2052	CA	TRP	A	270	81.768	24.975	-5.335	1.00	74.68	A	C
ATOM	2053	C	TRP	A	270	83.036	25.412	-6.065	1.00	75.66	A	C
ATOM	2054	O	TRP	A	270	83.455	26.563	-5.952	1.00	74.31	A	O
ATOM	2055	CB	TRP	A	270	80.584	25.108	-6.289	1.00	75.03	A	C
ATOM	2056	CG	TRP	A	270	79.330	24.451	-5.812	1.00	74.79	A	C
ATOM	2057	CD1	TRP	A	270	79.034	23.118	-5.848	1.00	74.58	A	C
ATOM	2058	CD2	TRP	A	270	78.191	25.099	-5.239	1.00	74.13	A	C
ATOM	2059	NE1	TRP	A	270	77.781	22.898	-5.329	1.00	74.78	A	N
ATOM	2060	CE2	TRP	A	270	77.241	24.098	-4.946	1.00	74.47	A	C
ATOM	2061	CE3	TRP	A	270	77.875	26.431	-4.939	1.00	73.49	A	C
ATOM	2062	CZ2	TRP	A	270	76.000	24.386	-4.372	1.00	74.22	A	C
ATOM	2063	CZ3	TRP	A	270	76.649	26.715	-4.371	1.00	73.73	A	C
ATOM	2064	CH2	TRP	A	270	75.727	25.696	-4.088	1.00	73.99	A	C
ATOM	2065	N	GLN	A	271	83.633	24.497	-6.827	1.00	77.31	A	N
ATOM	2066	CA	GLN	A	271	84.835	24.808	-7.603	1.00	78.64	A	C
ATOM	2067	C	GLN	A	271	84.559	25.956	-8.579	1.00	79.98	A	C
ATOM	2068	O	GLN	A	271	83.424	26.136	-9.025	1.00	79.95	A	O
ATOM	2069	CB	GLN	A	271	85.233	23.565	-8.378	1.00	78.38	A	C
ATOM	2070	CG	GLN	A	271	85.694	22.427	-7.461	0.00	20.00	A	C
ATOM	2071	CD	GLN	A	271	86.108	21.239	-8.297	0.00	20.00	A	C
ATOM	2072	OE1	GLN	A	271	86.517	20.197	-7.812	0.00	20.00	A	O
ATOM	2073	NE2	GLN	A	271	85.995	21.443	-9.624	0.00	20.00	A	N
ATOM	2074	N	ALA	A	272	85.596	26.733	-8.891	1.00	81.27	A	N
ATOM	2075	CA	ALA	A	272	85.467	27.927	-9.736	1.00	82.23	A	C
ATOM	2076	C	ALA	A	272	84.604	27.706	-10.989	1.00	82.74	A	C

ATOM	2077	O	ALA	A	272	85.006	27.012	-11.926	1.00	82.97	A	O
ATOM	2078	CB	ALA	A	272	86.850	28.443	-10.131	1.00	82.17	A	C
ATOM	2079	N	GLY	A	273	83.408	28.289	-10.977	1.00	83.80	A	N
ATOM	2080	CA	GLY	A	273	82.523	28.301	-12.132	1.00	84.66	A	C
ATOM	2081	C	GLY	A	273	81.761	27.008	-12.373	1.00	84.93	A	C
ATOM	2082	O	GLY	A	273	81.383	26.720	-13.511	1.00	86.15	A	O
ATOM	2083	N	THR	A	274	81.509	26.250	-11.305	1.00	84.63	A	N
ATOM	2084	CA	THR	A	274	80.861	24.940	-11.396	1.00	84.75	A	C
ATOM	2085	C	THR	A	274	79.570	24.921	-10.581	1.00	84.35	A	C
ATOM	2086	O	THR	A	274	79.158	23.880	-10.064	1.00	82.91	A	O
ATOM	2087	CB	THR	A	274	81.812	23.828	-10.895	1.00	85.61	A	C
ATOM	2088	OG1	THR	A	274	82.135	24.043	-9.514	1.00	85.37	A	O
ATOM	2089	CG2	THR	A	274	83.162	23.879	-11.618	1.00	86.24	A	C
ATOM	2090	N	THR	A	275	78.929	26.079	-10.480	1.00	84.51	A	N
ATOM	2091	CA	THR	A	275	77.719	26.213	-9.688	1.00	85.22	A	C
ATOM	2092	C	THR	A	275	76.535	25.616	-10.451	1.00	84.97	A	C
ATOM	2093	O	THR	A	275	76.311	25.959	-11.614	1.00	83.74	A	O
ATOM	2094	CB	THR	A	275	77.450	27.690	-9.370	1.00	85.63	A	C
ATOM	2095	OG1	THR	A	275	78.649	28.313	-8.889	1.00	87.20	A	O
ATOM	2096	CG2	THR	A	275	76.472	27.827	-8.210	1.00	86.40	A	C
ATOM	2097	N	PRO	A	276	75.790	24.718	-9.808	1.00	84.86	A	N
ATOM	2098	CA	PRO	A	276	74.591	24.138	-10.420	1.00	84.84	A	C
ATOM	2099	C	PRO	A	276	73.386	25.087	-10.330	1.00	84.60	A	C
ATOM	2100	O	PRO	A	276	72.759	25.213	-9.270	1.00	83.40	A	O
ATOM	2101	CB	PRO	A	276	74.363	22.864	-9.599	1.00	85.26	A	C
ATOM	2102	CG	PRO	A	276	74.945	23.160	-8.247	1.00	84.89	A	C
ATOM	2103	CD	PRO	A	276	76.033	24.178	-8.456	1.00	84.87	A	C
ATOM	2104	N	TRP	A	277	73.084	25.757	-11.441	1.00	83.87	A	N
ATOM	2105	CA	TRP	A	277	71.945	26.671	-11.512	1.00	82.59	A	C
ATOM	2106	C	TRP	A	277	70.645	25.914	-11.259	1.00	78.91	A	C
ATOM	2107	O	TRP	A	277	69.868	26.253	-10.361	1.00	76.37	A	O
ATOM	2108	CB	TRP	A	277	71.852	27.327	-12.903	1.00	84.62	A	C
ATOM	2109	CG	TRP	A	277	72.863	28.426	-13.258	1.00	86.23	A	C
ATOM	2110	CD1	TRP	A	277	73.299	28.743	-14.520	1.00	86.71	A	C
ATOM	2111	CD2	TRP	A	277	73.518	29.358	-12.371	1.00	86.55	A	C
ATOM	2112	NE1	TRP	A	277	74.186	29.792	-14.473	1.00	86.87	A	N
ATOM	2113	CE2	TRP	A	277	74.340	30.190	-13.171	1.00	87.19	A	C
ATOM	2114	CE3	TRP	A	277	73.503	29.573	-10.982	1.00	86.48	A	C
ATOM	2115	CZ2	TRP	A	277	75.129	31.211	-12.632	1.00	87.46	A	C
ATOM	2116	CZ3	TRP	A	277	74.291	30.587	-10.449	1.00	86.65	A	C
ATOM	2117	CH2	TRP	A	277	75.092	31.392	-11.273	1.00	87.15	A	C
ATOM	2118	N	ASN	A	278	70.450	24.864	-12.052	1.00	75.16	A	N
ATOM	2119	CA	ASN	A	278	69.149	24.232	-12.228	1.00	71.96	A	C
ATOM	2120	C	ASN	A	278	68.678	23.332	-11.094	1.00	68.53	A	C
ATOM	2121	O	ASN	A	278	67.516	22.952	-11.057	1.00	65.41	A	O
ATOM	2122	CB	ASN	A	278	69.145	23.456	-13.544	1.00	71.99	A	C
ATOM	2123	CG	ASN	A	278	69.124	24.372	-14.749	1.00	73.02	A	C
ATOM	2124	OD1	ASN	A	278	68.090	24.528	-15.397	1.00	75.67	A	O
ATOM	2125	ND2	ASN	A	278	70.261	25.002	-15.043	1.00	71.03	A	N
ATOM	2126	N	ILE	A	279	69.567	23.002	-10.164	1.00	67.52	A	N
ATOM	2127	CA	ILE	A	279	69.188	22.191	-9.006	1.00	66.60	A	C
ATOM	2128	C	ILE	A	279	68.277	22.978	-8.046	1.00	63.12	A	C
ATOM	2129	O	ILE	A	279	67.509	22.382	-7.293	1.00	61.43	A	O
ATOM	2130	CB	ILE	A	279	70.451	21.673	-8.266	1.00	69.14	A	C
ATOM	2131	CG1	ILE	A	279	71.311	20.801	-9.196	1.00	70.33	A	C
ATOM	2132	CG2	ILE	A	279	70.069	20.890	-7.004	1.00	70.79	A	C
ATOM	2133	CD1	ILE	A	279	70.601	19.582	-9.773	1.00	71.75	A	C
ATOM	2134	N	PHE	A	280	68.364	24.310	-8.089	1.00	58.16	A	N
ATOM	2135	CA	PHE	A	280	67.577	25.184	-7.215	1.00	54.73	A	C
ATOM	2136	C	PHE	A	280	66.327	25.723	-7.929	1.00	48.44	A	C
ATOM	2137	O	PHE	A	280	66.404	26.160	-9.065	1.00	42.63	A	O
ATOM	2138	CB	PHE	A	280	68.440	26.352	-6.737	1.00	54.07	A	C
ATOM	2139	CG	PHE	A	280	69.641	25.934	-5.950	1.00	56.01	A	C
ATOM	2140	CD1	PHE	A	280	70.860	25.735	-6.582	1.00	56.28	A	C
ATOM	2141	CD2	PHE	A	280	69.554	25.741	-4.578	1.00	56.86	A	C
ATOM	2142	CE1	PHE	A	280	71.975	25.351	-5.861	1.00	58.79	A	C
ATOM	2143	CE2	PHE	A	280	70.663	25.351	-3.846	1.00	58.48	A	C
ATOM	2144	CZ	PHE	A	280	71.880	25.158	-4.487	1.00	58.24	A	C
ATOM	2145	N	PRO	A	281	65.183	25.713	-7.253	1.00	46.45	A	N
ATOM	2146	CA	PRO	A	281	63.933	26.153	-7.873	1.00	45.34	A	C
ATOM	2147	C	PRO	A	281	63.830	27.670	-7.930	1.00	46.32	A	C
ATOM	2148	O	PRO	A	281	64.540	28.377	-7.209	1.00	44.85	A	O
ATOM	2149	CB	PRO	A	281	62.875	25.625	-6.911	1.00	47.02	A	C
ATOM	2150	CG	PRO	A	281	63.552	25.707	-5.574	1.00	48.68	A	C
ATOM	2151	CD	PRO	A	281	64.985	25.312	-5.845	1.00	47.62	A	C
ATOM	2152	N	VAL	A	282	62.942	28.158	-8.783	1.00	44.02	A	N
ATOM	2153	CA	VAL	A	282	62.594	29.567	-8.785	1.00	44.12	A	C

ATOM	2154	C	VAL	A	282	61.625	29.811	-7.650	1.00	44.35	A	C
ATOM	2155	O	VAL	A	282	60.976	28.886	-7.174	1.00	43.30	A	O
ATOM	2156	CB	VAL	A	282	61.977	30.021	-10.119	1.00	44.10	A	C
ATOM	2157	CG1	VAL	A	282	62.930	29.754	-11.259	1.00	40.34	A	C
ATOM	2158	CG2	VAL	A	282	60.621	29.359	-10.368	1.00	48.29	A	C
ATOM	2159	N	ILE	A	283	61.555	31.048	-7.186	1.00	40.14	A	N
ATOM	2160	CA	ILE	A	283	60.502	31.421	-6.273	1.00	42.52	A	C
ATOM	2161	C	ILE	A	283	59.656	32.479	-6.970	1.00	39.13	A	C
ATOM	2162	O	ILE	A	283	60.171	33.297	-7.743	1.00	35.09	A	O
ATOM	2163	CB	ILE	A	283	61.043	31.847	-4.878	1.00	43.69	A	C
ATOM	2164	CG1	ILE	A	283	59.925	32.432	-4.023	1.00	46.75	A	C
ATOM	2165	CG2	ILE	A	283	62.174	32.818	-4.984	1.00	47.57	A	C
ATOM	2166	CD1	ILE	A	283	60.216	32.406	-2.547	1.00	47.98	A	C
ATOM	2167	N	SER	A	284	58.350	32.359	-6.758	1.00	35.81	A	N
ATOM	2168	CA	SER	A	284	57.354	33.282	-7.292	1.00	33.91	A	C
ATOM	2169	C	SER	A	284	56.555	33.814	-6.121	1.00	32.23	A	C
ATOM	2170	O	SER	A	284	56.080	33.051	-5.274	1.00	31.03	A	O
ATOM	2171	CB	SER	A	284	56.457	32.574	-8.313	1.00	31.65	A	C
ATOM	2172	OG	SER	A	284	57.075	32.546	-9.585	1.00	35.60	A	O
ATOM	2173	N	LEU	A	285	56.455	35.137	-6.028	1.00	25.42	A	N
ATOM	2174	CA	LEU	A	285	55.588	35.760	-5.069	1.00	24.59	A	C
ATOM	2175	C	LEU	A	285	54.478	36.397	-5.890	1.00	21.13	A	C
ATOM	2176	O	LEU	A	285	54.770	37.108	-6.839	1.00	19.53	A	O
ATOM	2177	CB	LEU	A	285	56.348	36.799	-4.263	1.00	27.87	A	C
ATOM	2178	CG	LEU	A	285	57.674	36.297	-3.682	1.00	27.04	A	C
ATOM	2179	CD1	LEU	A	285	58.356	37.456	-3.002	1.00	31.32	A	C
ATOM	2180	CD2	LEU	A	285	57.428	35.159	-2.702	1.00	29.67	A	C
ATOM	2181	N	TYR	A	286	53.233	36.065	-5.587	1.00	22.23	A	N
ATOM	2182	CA	TYR	A	286	52.112	36.768	-6.196	1.00	22.87	A	C
ATOM	2183	C	TYR	A	286	51.807	37.909	-5.280	1.00	20.51	A	C
ATOM	2184	O	TYR	A	286	51.686	37.712	-4.069	1.00	23.12	A	O
ATOM	2185	CB	TYR	A	286	50.871	35.898	-6.336	1.00	18.84	A	C
ATOM	2186	CG	TYR	A	286	50.989	34.755	-7.339	1.00	20.36	A	C
ATOM	2187	CD1	TYR	A	286	51.857	33.691	-7.125	1.00	27.97	A	C
ATOM	2188	CD2	TYR	A	286	50.168	34.720	-8.477	1.00	22.74	A	C
ATOM	2189	CE1	TYR	A	286	51.937	32.641	-8.024	1.00	28.14	A	C
ATOM	2190	CE2	TYR	A	286	50.243	33.661	-9.393	1.00	19.26	A	C
ATOM	2191	CZ	TYR	A	286	51.125	32.630	-9.148	1.00	24.29	A	C
ATOM	2192	OH	TYR	A	286	51.198	31.595	-10.033	1.00	23.89	A	O
ATOM	2193	N	LEU	A	287	51.672	39.113	-5.849	1.00	17.57	A	N
ATOM	2194	CA	LEU	A	287	51.327	40.293	-5.084	1.00	18.37	A	C
ATOM	2195	C	LEU	A	287	49.902	40.714	-5.367	1.00	19.30	A	C
ATOM	2196	O	LEU	A	287	49.413	40.525	-6.486	1.00	17.31	A	O
ATOM	2197	CB	LEU	A	287	52.291	41.429	-5.435	1.00	16.99	A	C
ATOM	2198	CG	LEU	A	287	53.759	41.076	-5.143	1.00	19.76	A	C
ATOM	2199	CD1	LEU	A	287	54.689	42.131	-5.672	1.00	21.23	A	C
ATOM	2200	CD2	LEU	A	287	53.943	40.852	-3.653	1.00	27.06	A	C
ATOM	2201	N	MET	A	288	49.250	41.310	-4.369	1.00	17.49	A	N
ATOM	2202	CA	MET	A	288	47.906	41.869	-4.524	1.00	14.88	A	C
ATOM	2203	C	MET	A	288	47.938	42.861	-5.688	1.00	17.43	A	C
ATOM	2204	O	MET	A	288	48.833	43.675	-5.798	1.00	16.72	A	O
ATOM	2205	CB	MET	A	288	47.471	42.597	-3.242	1.00	19.44	A	C
ATOM	2206	CG	MET	A	288	46.150	43.315	-3.360	1.00	21.18	A	C
ATOM	2207	SD	MET	A	288	45.656	44.123	-1.787	1.00	27.75	A	S
ATOM	2208	CE	MET	A	288	45.045	42.809	-0.930	1.00	26.84	A	C
ATOM	2209	N	GLY	A	289	46.961	42.792	-6.574	1.00	15.66	A	N
ATOM	2210	CA	GLY	A	289	46.942	43.753	-7.664	1.00	17.02	A	C
ATOM	2211	C	GLY	A	289	46.143	45.000	-7.381	1.00	16.69	A	C
ATOM	2212	O	GLY	A	289	45.655	45.211	-6.267	1.00	16.95	A	O
ATOM	2213	N	GLU	A	290	45.922	45.786	-8.425	1.00	16.66	A	N
ATOM	2214	CA	GLU	A	290	45.190	47.057	-8.298	1.00	17.93	A	C
ATOM	2215	C	GLU	A	290	43.656	46.888	-8.251	1.00	18.47	A	C
ATOM	2216	O	GLU	A	290	42.944	47.782	-7.800	1.00	20.92	A	O
ATOM	2217	CB	GLU	A	290	45.541	47.958	-9.465	1.00	21.26	A	C
ATOM	2218	CG	GLU	A	290	47.003	48.349	-9.525	1.00	21.77	A	C
ATOM	2219	CD	GLU	A	290	47.243	49.526	-10.450	1.00	21.06	A	C
ATOM	2220	OE1	GLU	A	290	47.442	49.321	-11.696	1.00	22.85	A	O
ATOM	2221	OE2	GLU	A	290	47.229	50.657	-9.934	1.00	23.70	A	O
ATOM	2222	N	VAL	A	291	43.175	45.765	-8.763	1.00	19.67	A	N
ATOM	2223	CA	VAL	A	291	41.752	45.506	-8.963	1.00	19.72	A	C
ATOM	2224	C	VAL	A	291	41.323	44.329	-8.092	1.00	18.87	A	C
ATOM	2225	O	VAL	A	291	42.084	43.384	-7.867	1.00	18.96	A	O
ATOM	2226	CB	VAL	A	291	41.488	45.199	-10.467	1.00	20.83	A	C
ATOM	2227	CG1	VAL	A	291	40.050	44.761	-10.722	1.00	24.34	A	C
ATOM	2228	CG2	VAL	A	291	41.848	46.419	-11.311	1.00	20.67	A	C
ATOM	2229	N	THR	A	292	40.088	44.379	-7.592	1.00	19.56	A	N
ATOM	2230	CA	THR	A	292	39.548	43.301	-6.774	1.00	20.18	A	C

ATOM	2231	C	THR	A	292	39.725	41.949	-7.445	1.00	20.54	A	C
ATOM	2232	O	THR	A	292	39.429	41.803	-8.610	1.00	17.81	A	O
ATOM	2233	CB	THR	A	292	38.068	43.581	-6.524	1.00	23.16	A	C
ATOM	2234	OG1	THR	A	292	37.967	44.736	-5.684	1.00	26.50	A	O
ATOM	2235	CG2	THR	A	292	37.402	42.452	-5.738	1.00	25.56	A	C
ATOM	2236	N	ASN	A	293	40.209	40.975	-6.689	1.00	18.34	A	N
ATOM	2237	CA	ASN	A	293	40.397	39.597	-7.126	1.00	19.39	A	C
ATOM	2238	C	ASN	A	293	41.474	39.420	-8.218	1.00	20.71	A	C
ATOM	2239	O	ASN	A	293	41.536	38.375	-8.822	1.00	19.32	A	O
ATOM	2240	CB	ASN	A	293	39.066	38.968	-7.579	1.00	18.84	A	C
ATOM	2241	CG	ASN	A	293	38.142	38.594	-6.414	1.00	23.11	A	C
ATOM	2242	OD1	ASN	A	293	38.573	38.422	-5.267	1.00	24.46	A	O
ATOM	2243	ND2	ASN	A	293	36.863	38.438	-6.724	1.00	24.82	A	N
ATOM	2244	N	GLN	A	294	42.338	40.424	-8.416	1.00	20.83	A	N
ATOM	2245	CA	GLN	A	294	43.381	40.392	-9.443	1.00	16.07	A	C
ATOM	2246	C	GLN	A	294	44.748	40.529	-8.794	1.00	18.30	A	C
ATOM	2247	O	GLN	A	294	44.968	41.445	-8.011	1.00	19.08	A	O
ATOM	2248	CB	GLN	A	294	43.178	41.537	-10.438	1.00	16.09	A	C
ATOM	2249	CG	GLN	A	294	44.307	41.763	-11.435	1.00	14.15	A	C
ATOM	2250	CD	GLN	A	294	45.315	42.825	-10.969	1.00	15.00	A	C
ATOM	2251	OE1	GLN	A	294	44.928	43.902	-10.501	1.00	17.11	A	O
ATOM	2252	NE2	GLN	A	294	46.599	42.514	-11.111	1.00	12.44	A	N
ATOM	2253	N	SER	A	295	45.645	39.617	-9.146	1.00	17.25	A	N
ATOM	2254	CA	SER	A	295	47.016	39.617	-8.650	1.00	17.43	A	C
ATOM	2255	C	SER	A	295	47.979	39.581	-9.840	1.00	18.06	A	C
ATOM	2256	O	SER	A	295	47.556	39.486	-10.992	1.00	16.54	A	O
ATOM	2257	CB	SER	A	295	47.247	38.420	-7.738	1.00	16.97	A	C
ATOM	2258	OG	SER	A	295	47.161	37.211	-8.475	1.00	17.63	A	O
ATOM	2259	N	PHE	A	296	49.279	39.722	-9.563	1.00	13.70	A	N
ATOM	2260	CA	PHE	A	296	50.326	39.457	-10.543	1.00	16.16	A	C
ATOM	2261	C	PHE	A	296	51.456	38.721	-9.823	1.00	17.11	A	C
ATOM	2262	O	PHE	A	296	51.463	38.654	-8.612	1.00	14.83	A	O
ATOM	2263	CB	PHE	A	296	50.833	40.734	-11.217	1.00	16.09	A	C
ATOM	2264	CG	PHE	A	296	51.510	41.703	-10.290	1.00	13.78	A	C
ATOM	2265	CD1	PHE	A	296	50.757	42.537	-9.504	1.00	12.99	A	C
ATOM	2266	CD2	PHE	A	296	52.888	41.759	-10.202	1.00	16.17	A	C
ATOM	2267	CE1	PHE	A	296	51.359	43.451	-8.653	1.00	15.39	A	C
ATOM	2268	CE2	PHE	A	296	53.502	42.693	-9.339	1.00	12.59	A	C
ATOM	2269	CZ	PHE	A	296	52.718	43.519	-8.580	1.00	15.93	A	C
ATOM	2270	N	ARG	A	297	52.388	38.150	-10.564	1.00	18.57	A	N
ATOM	2271	CA	ARG	A	297	53.501	37.470	-9.908	1.00	21.97	A	C
ATOM	2272	C	ARG	A	297	54.830	37.955	-10.429	1.00	19.76	A	C
ATOM	2273	O	ARG	A	297	54.990	38.238	-11.612	1.00	20.21	A	O
ATOM	2274	CB	ARG	A	297	53.391	35.959	-10.045	1.00	27.12	A	C
ATOM	2275	CG	ARG	A	297	53.915	35.442	-11.323	1.00	25.39	A	C
ATOM	2276	CD	ARG	A	297	53.887	33.904	-11.434	1.00	28.85	A	C
ATOM	2277	NE	ARG	A	297	54.152	33.532	-12.810	1.00	28.07	A	N
ATOM	2278	CZ	ARG	A	297	53.625	32.493	-13.435	1.00	29.23	A	C
ATOM	2279	NH1	ARG	A	297	52.808	31.664	-12.800	1.00	29.79	A	N
ATOM	2280	NH2	ARG	A	297	53.942	32.273	-14.708	1.00	33.36	A	N
ATOM	2281	N	ILE	A	298	55.769	38.034	-9.501	1.00	22.62	A	N
ATOM	2282	CA	ILE	A	298	57.171	38.264	-9.776	1.00	22.52	A	C
ATOM	2283	C	ILE	A	298	57.926	36.968	-9.461	1.00	20.35	A	C
ATOM	2284	O	ILE	A	298	57.616	36.268	-8.498	1.00	24.62	A	O
ATOM	2285	CB	ILE	A	298	57.700	39.494	-8.963	1.00	20.28	A	C
ATOM	2286	CG1	ILE	A	298	57.778	39.216	-7.453	1.00	21.96	A	C
ATOM	2287	CG2	ILE	A	298	56.838	40.708	-9.257	1.00	20.40	A	C
ATOM	2288	CD1	ILE	A	298	58.375	40.390	-6.628	1.00	19.78	A	C
ATOM	2289	N	THR	A	299	58.900	36.671	-10.297	1.00	27.12	A	N
ATOM	2290	CA	THR	A	299	59.621	35.404	-10.271	1.00	27.28	A	C
ATOM	2291	C	THR	A	299	61.114	35.702	-10.229	1.00	26.61	A	C
ATOM	2292	O	THR	A	299	61.614	36.337	-11.139	1.00	28.84	A	O
ATOM	2293	CB	THR	A	299	59.291	34.640	-11.560	1.00	27.03	A	C
ATOM	2294	OG1	THR	A	299	57.902	34.287	-11.572	1.00	32.46	A	O
ATOM	2295	CG2	THR	A	299	60.001	33.283	-11.620	1.00	28.77	A	C
ATOM	2296	N	ILE	A	300	61.803	35.268	-9.175	1.00	31.26	A	N
ATOM	2297	CA	ILE	A	300	63.270	35.393	-9.098	1.00	33.70	A	C
ATOM	2298	C	ILE	A	300	63.938	34.033	-9.195	1.00	39.02	A	C
ATOM	2299	O	ILE	A	300	63.273	32.989	-9.287	1.00	37.86	A	O
ATOM	2300	CB	ILE	A	300	63.729	36.107	-7.793	1.00	35.95	A	C
ATOM	2301	CG1	ILE	A	300	63.443	35.258	-6.566	1.00	37.33	A	C
ATOM	2302	CG2	ILE	A	300	63.049	37.457	-7.639	1.00	35.67	A	C
ATOM	2303	CD1	ILE	A	300	64.152	35.715	-5.318	1.00	39.22	A	C
ATOM	2304	N	LEU	A	301	65.265	34.067	-9.161	1.00	39.05	A	N
ATOM	2305	CA	LEU	A	301	66.093	32.901	-9.421	1.00	37.54	A	C
ATOM	2306	C	LEU	A	301	67.013	32.602	-8.255	1.00	38.40	A	C
ATOM	2307	O	LEU	A	301	67.182	33.428	-7.371	1.00	36.53	A	O

ATOM	2308	CB	LEU	A	301	66.933	33.169	-10.664	1.00	36.30	A	C
ATOM	2309	CG	LEU	A	301	66.126	33.447	-11.937	1.00	34.74	A	C
ATOM	2310	CD1	LEU	A	301	67.030	33.935	-13.022	1.00	32.47	A	C
ATOM	2311	CD2	LEU	A	301	65.387	32.196	-12.430	1.00	39.84	A	C
ATOM	2312	N	PRO	A	302	67.619	31.420	-8.264	1.00	39.73	A	N
ATOM	2313	CA	PRO	A	302	68.706	31.113	-7.335	1.00	41.84	A	C
ATOM	2314	C	PRO	A	302	69.828	32.157	-7.387	1.00	41.87	A	C
ATOM	2315	O	PRO	A	302	70.427	32.420	-6.356	1.00	45.40	A	O
ATOM	2316	CB	PRO	A	302	69.208	29.759	-7.834	1.00	41.99	A	C
ATOM	2317	CG	PRO	A	302	68.031	29.157	-8.495	1.00	42.63	A	C
ATOM	2318	CD	PRO	A	302	67.321	30.285	-9.150	1.00	40.17	A	C
ATOM	2319	N	GLN	A	303	70.094	32.759	-8.546	1.00	40.21	A	N
ATOM	2320	CA	GLN	A	303	71.197	33.721	-8.659	1.00	41.56	A	C
ATOM	2321	C	GLN	A	303	70.933	34.984	-7.824	1.00	43.24	A	C
ATOM	2322	O	GLN	A	303	71.837	35.788	-7.598	1.00	38.56	A	O
ATOM	2323	CB	GLN	A	303	71.523	34.117	-10.119	1.00	44.66	A	C
ATOM	2324	CG	GLN	A	303	70.564	33.666	-11.201	1.00	47.40	A	C
ATOM	2325	CD	GLN	A	303	70.716	32.201	-11.545	1.00	50.63	A	C
ATOM	2326	OE1	GLN	A	303	69.911	31.372	-11.120	1.00	55.64	A	O
ATOM	2327	NE2	GLN	A	303	71.742	31.877	-12.332	1.00	51.86	A	N
ATOM	2328	N	GLN	A	304	69.689	35.145	-7.382	1.00	41.50	A	N
ATOM	2329	CA	GLN	A	304	69.273	36.282	-6.589	1.00	46.43	A	C
ATOM	2330	C	GLN	A	304	69.293	35.906	-5.100	1.00	47.20	A	C
ATOM	2331	O	GLN	A	304	69.738	36.705	-4.270	1.00	45.43	A	O
ATOM	2332	CB	GLN	A	304	67.871	36.735	-7.046	1.00	49.88	A	C
ATOM	2333	CG	GLN	A	304	67.862	37.811	-8.157	1.00	51.33	A	C
ATOM	2334	CD	GLN	A	304	68.273	37.315	-9.548	1.00	54.63	A	C
ATOM	2335	OE1	GLN	A	304	67.918	37.933	-10.556	1.00	54.99	A	O
ATOM	2336	NE2	GLN	A	304	69.031	36.224	-9.607	1.00	57.60	A	N
ATOM	2337	N	TYR	A	305	68.838	34.694	-4.760	1.00	47.73	A	N
ATOM	2338	CA	TYR	A	305	68.895	34.241	-3.364	1.00	51.85	A	C
ATOM	2339	C	TYR	A	305	70.132	33.385	-3.029	1.00	53.38	A	C
ATOM	2340	O	TYR	A	305	70.267	32.911	-1.903	1.00	53.57	A	O
ATOM	2341	CB	TYR	A	305	67.573	33.577	-2.910	1.00	52.81	A	C
ATOM	2342	CG	TYR	A	305	67.247	32.202	-3.471	1.00	53.16	A	C
ATOM	2343	CD1	TYR	A	305	67.828	31.052	-2.943	1.00	52.42	A	C
ATOM	2344	CD2	TYR	A	305	66.309	32.053	-4.494	1.00	52.93	A	C
ATOM	2345	CE1	TYR	A	305	67.515	29.789	-3.446	1.00	53.23	A	C
ATOM	2346	CE2	TYR	A	305	65.985	30.796	-5.002	1.00	53.91	A	C
ATOM	2347	CZ	TYR	A	305	66.592	29.669	-4.474	1.00	53.62	A	C
ATOM	2348	OH	TYR	A	305	66.272	28.425	-4.971	1.00	53.84	A	O
ATOM	2349	N	LEU	A	306	71.033	33.228	-3.997	1.00	55.03	A	N
ATOM	2350	CA	LEU	A	306	72.355	32.633	-3.777	1.00	61.56	A	C
ATOM	2351	C	LEU	A	306	73.390	33.700	-4.150	1.00	63.69	A	C
ATOM	2352	O	LEU	A	306	73.663	33.946	-5.332	1.00	64.04	A	O
ATOM	2353	CB	LEU	A	306	72.559	31.361	-4.610	1.00	62.70	A	C
ATOM	2354	CG	LEU	A	306	72.418	29.992	-3.934	1.00	65.11	A	C
ATOM	2355	CD1	LEU	A	306	71.256	29.932	-2.950	1.00	65.92	A	C
ATOM	2356	CD2	LEU	A	306	72.262	28.920	-5.001	1.00	65.99	A	C
ATOM	2357	N	ARG	A	307	73.965	34.321	-3.126	1.00	67.42	A	N
ATOM	2358	CA	ARG	A	307	74.753	35.546	-3.285	1.00	69.54	A	C
ATOM	2359	C	ARG	A	307	76.226	35.241	-3.045	1.00	70.36	A	C
ATOM	2360	O	ARG	A	307	76.568	34.726	-1.981	1.00	69.95	A	O
ATOM	2361	CB	ARG	A	307	74.270	36.631	-2.302	1.00	70.52	A	C
ATOM	2362	CG	ARG	A	307	73.942	36.126	-0.885	1.00	71.76	A	C
ATOM	2363	CD	ARG	A	307	73.347	37.158	0.060	1.00	71.91	A	C
ATOM	2364	NE	ARG	A	307	74.308	37.604	1.064	1.00	71.58	A	N
ATOM	2365	CZ	ARG	A	307	75.160	38.609	0.900	1.00	72.31	A	C
ATOM	2366	NH1	ARG	A	307	75.184	39.300	-0.239	1.00	72.16	A	N
ATOM	2367	NH2	ARG	A	307	75.998	38.930	1.882	1.00	72.17	A	N
ATOM	2368	N	PRO	A	308	77.095	35.520	-4.022	1.00	71.45	A	N
ATOM	2369	CA	PRO	A	308	78.544	35.396	-3.809	1.00	72.19	A	C
ATOM	2370	C	PRO	A	308	79.011	36.173	-2.576	1.00	73.28	A	C
ATOM	2371	O	PRO	A	308	78.712	37.362	-2.461	1.00	73.54	A	O
ATOM	2372	CB	PRO	A	308	79.144	35.999	-5.089	1.00	72.26	A	C
ATOM	2373	CG	PRO	A	308	78.083	35.844	-6.123	1.00	71.35	A	C
ATOM	2374	CD	PRO	A	308	76.775	35.937	-5.400	1.00	71.33	A	C
ATOM	2375	N	VAL	A	309	79.698	35.500	-1.656	1.00	75.03	A	N
ATOM	2376	CA	VAL	A	309	80.253	36.151	-0.472	1.00	77.51	A	C
ATOM	2377	C	VAL	A	309	81.604	36.759	-0.842	1.00	79.98	A	C
ATOM	2378	O	VAL	A	309	82.613	36.051	-0.877	1.00	79.39	A	O
ATOM	2379	CB	VAL	A	309	80.412	35.162	0.708	1.00	77.15	A	C
ATOM	2380	CG1	VAL	A	309	81.097	35.838	1.896	1.00	76.95	A	C
ATOM	2381	CG2	VAL	A	309	79.056	34.605	1.118	1.00	76.88	A	C
ATOM	2382	N	GLU	A	310	81.596	38.065	-1.130	1.00	83.03	A	N
ATOM	2383	CA	GLU	A	310	82.777	38.833	-1.562	1.00	84.93	A	C
ATOM	2384	C	GLU	A	310	83.980	37.940	-1.953	1.00	86.11	A	C

ATOM	2385	O	GLU	A	310	83.862	37.110	-2.864	1.00	85.97	A	O
ATOM	2386	CB	GLU	A	310	83.131	39.882	-0.488	1.00	85.41	A	C
ATOM	2387	CG	GLU	A	310	83.937	41.076	-0.997	1.00	86.20	A	C
ATOM	2388	CD	GLU	A	310	83.130	42.368	-1.053	1.00	87.05	A	C
ATOM	2389	OE1	GLU	A	310	82.756	42.794	-2.166	1.00	86.88	A	O
ATOM	2390	OE2	GLU	A	310	82.873	42.962	0.018	1.00	87.99	A	O
ATOM	2391	N	ASP	A	311	85.130	38.129	-1.304	1.00	86.94	A	N
ATOM	2392	CA	ASP	A	311	86.230	37.175	-1.390	1.00	87.73	A	C
ATOM	2393	C	ASP	A	311	86.260	36.411	-0.071	1.00	88.09	A	C
ATOM	2394	O	ASP	A	311	85.615	36.817	0.902	1.00	87.73	A	O
ATOM	2395	CB	ASP	A	311	87.580	37.879	-1.616	1.00	88.63	A	C
ATOM	2396	CG	ASP	A	311	87.502	39.029	-2.619	1.00	89.53	A	C
ATOM	2397	OD1	ASP	A	311	88.543	39.686	-2.848	1.00	90.31	A	O
ATOM	2398	OD2	ASP	A	311	86.457	39.356	-3.222	1.00	90.95	A	O
ATOM	2399	N	VAL	A	312	86.995	35.302	-0.043	1.00	88.24	A	N
ATOM	2400	CA	VAL	A	312	87.233	34.565	1.201	1.00	88.26	A	C
ATOM	2401	C	VAL	A	312	88.737	34.311	1.376	1.00	88.60	A	C
ATOM	2402	O	VAL	A	312	89.440	33.985	0.414	1.00	88.89	A	O
ATOM	2403	CB	VAL	A	312	86.407	33.238	1.271	1.00	87.95	A	C
ATOM	2404	CG1	VAL	A	312	84.949	33.489	0.890	1.00	87.35	A	C
ATOM	2405	CG2	VAL	A	312	87.009	32.145	0.392	1.00	87.59	A	C
ATOM	2406	N	ALA	A	313	89.218	34.475	2.608	1.00	88.84	A	N
ATOM	2407	CA	ALA	A	313	90.649	34.372	2.916	1.00	88.57	A	C
ATOM	2408	C	ALA	A	313	91.138	32.925	3.070	1.00	88.37	A	C
ATOM	2409	O	ALA	A	313	92.311	32.633	2.816	1.00	88.18	A	O
ATOM	2410	CB	ALA	A	313	90.965	35.166	4.176	1.00	88.37	A	C
ATOM	2411	N	THR	A	314	90.236	32.029	3.478	1.00	88.05	A	N
ATOM	2412	CA	THR	A	314	90.576	30.625	3.735	1.00	87.53	A	C
ATOM	2413	C	THR	A	314	90.165	29.692	2.581	1.00	87.78	A	C
ATOM	2414	O	THR	A	314	90.059	28.474	2.768	1.00	87.87	A	O
ATOM	2415	CB	THR	A	314	89.941	30.148	5.079	1.00	87.19	A	C
ATOM	2416	OG1	THR	A	314	88.581	30.591	5.184	1.00	86.46	A	O
ATOM	2417	CG2	THR	A	314	90.631	30.799	6.276	1.00	86.98	A	C
ATOM	2418	N	SER	A	315	89.946	30.262	1.393	1.00	87.13	A	N
ATOM	2419	CA	SER	A	315	89.610	29.484	0.194	1.00	86.43	A	C
ATOM	2420	C	SER	A	315	89.806	30.289	-1.099	1.00	85.61	A	C
ATOM	2421	O	SER	A	315	90.082	31.491	-1.061	1.00	85.17	A	O
ATOM	2422	CB	SER	A	315	88.161	28.971	0.268	1.00	86.53	A	C
ATOM	2423	OG	SER	A	315	88.053	27.650	-0.240	1.00	86.72	A	O
ATOM	2424	N	GLN	A	316	89.666	29.609	-2.238	1.00	84.67	A	N
ATOM	2425	CA	GLN	A	316	89.668	30.261	-3.551	1.00	83.71	A	C
ATOM	2426	C	GLN	A	316	88.529	29.737	-4.435	1.00	82.54	A	C
ATOM	2427	O	GLN	A	316	88.656	29.684	-5.660	1.00	83.13	A	O
ATOM	2428	CB	GLN	A	316	91.021	30.062	-4.242	1.00	83.88	A	C
ATOM	2429	CG	GLN	A	316	91.420	31.209	-5.162	1.00	84.53	A	C
ATOM	2430	CD	GLN	A	316	91.981	32.399	-4.402	1.00	85.47	A	C
ATOM	2431	OE1	GLN	A	316	91.229	33.262	-3.946	1.00	86.70	A	O
ATOM	2432	NE2	GLN	A	316	93.302	32.444	-4.259	1.00	85.53	A	N
ATOM	2433	N	ASP	A	317	87.413	29.374	-3.800	1.00	81.34	A	N
ATOM	2434	CA	ASP	A	317	86.250	28.806	-4.486	1.00	80.52	A	C
ATOM	2435	C	ASP	A	317	85.150	29.855	-4.659	1.00	79.03	A	C
ATOM	2436	O	ASP	A	317	85.250	30.958	-4.121	1.00	79.27	A	O
ATOM	2437	CB	ASP	A	317	85.696	27.619	-3.683	1.00	81.10	A	C
ATOM	2438	CG	ASP	A	317	86.445	26.327	-3.945	1.00	81.61	A	C
ATOM	2439	OD1	ASP	A	317	85.860	25.251	-3.706	1.00	82.22	A	O
ATOM	2440	OD2	ASP	A	317	87.616	26.284	-4.381	1.00	83.59	A	O
ATOM	2441	N	ASP	A	318	84.113	29.504	-5.421	1.00	77.10	A	N
ATOM	2442	CA	ASP	A	318	82.894	30.315	-5.525	1.00	76.86	A	C
ATOM	2443	C	ASP	A	318	81.909	29.982	-4.398	1.00	75.04	A	C
ATOM	2444	O	ASP	A	318	81.025	29.137	-4.565	1.00	76.20	A	O
ATOM	2445	CB	ASP	A	318	82.212	30.093	-6.880	1.00	76.77	A	C
ATOM	2446	CG	ASP	A	318	83.043	30.590	-8.044	1.00	77.69	A	C
ATOM	2447	OD1	ASP	A	318	84.270	30.781	-7.874	1.00	78.53	A	O
ATOM	2448	OD2	ASP	A	318	82.550	30.811	-9.170	1.00	77.17	A	O
ATOM	2449	N	CYS	A	319	82.065	30.653	-3.259	1.00	73.01	A	N
ATOM	2450	CA	CYS	A	319	81.211	30.428	-2.094	1.00	71.05	A	C
ATOM	2451	C	CYS	A	319	80.044	31.414	-2.062	1.00	68.67	A	C
ATOM	2452	O	CYS	A	319	80.235	32.611	-2.258	1.00	66.66	A	O
ATOM	2453	CB	CYS	A	319	82.026	30.554	-0.803	1.00	71.92	A	C
ATOM	2454	SG	CYS	A	319	83.414	29.394	-0.686	1.00	74.09	A	S
ATOM	2455	N	TYR	A	320	78.839	30.899	-1.832	1.00	66.44	A	N
ATOM	2456	CA	TYR	A	320	77.645	31.728	-1.691	1.00	64.22	A	C
ATOM	2457	C	TYR	A	320	77.013	31.498	-0.320	1.00	62.66	A	C
ATOM	2458	O	TYR	A	320	77.332	30.523	0.365	1.00	61.41	A	O
ATOM	2459	CB	TYR	A	320	76.611	31.384	-2.764	1.00	64.24	A	C
ATOM	2460	CG	TYR	A	320	77.108	31.323	-4.198	1.00	64.74	A	C
ATOM	2461	CD1	TYR	A	320	77.957	30.302	-4.632	1.00	64.73	A	C

ATOM	2462	CD2	TYR	A	320	76.682	32.260	-5.139	1.00	64.78	A	C
ATOM	2463	CE1	TYR	A	320	78.390	30.239	-5.961	1.00	64.57	A	C
ATOM	2464	CE2	TYR	A	320	77.106	32.202	-6.465	1.00	64.30	A	C
ATOM	2465	CZ	TYR	A	320	77.957	31.193	-6.871	1.00	64.35	A	C
ATOM	2466	OH	TYR	A	320	78.374	31.146	-8.185	1.00	62.89	A	O
ATOM	2467	N	LYS	A	321	76.111	32.392	0.076	1.00	59.11	A	N
ATOM	2468	CA	LYS	A	321	75.320	32.189	1.286	1.00	58.36	A	C
ATOM	2469	C	LYS	A	321	73.816	32.265	0.996	1.00	55.24	A	C
ATOM	2470	O	LYS	A	321	73.353	33.065	0.181	1.00	47.87	A	O
ATOM	2471	CB	LYS	A	321	75.747	33.160	2.398	1.00	59.88	A	C
ATOM	2472	CG	LYS	A	321	74.853	34.371	2.629	1.00	62.72	A	C
ATOM	2473	CD	LYS	A	321	75.277	35.120	3.888	1.00	64.37	A	C
ATOM	2474	CE	LYS	A	321	74.699	34.483	5.145	1.00	64.91	A	C
ATOM	2475	NZ	LYS	A	321	74.999	35.289	6.363	1.00	66.23	A	N
ATOM	2476	N	PHE	A	322	73.062	31.401	1.664	1.00	51.88	A	N
ATOM	2477	CA	PHE	A	322	71.619	31.397	1.531	1.00	49.73	A	C
ATOM	2478	C	PHE	A	322	71.087	32.737	2.019	1.00	49.06	A	C
ATOM	2479	O	PHE	A	322	71.346	33.148	3.154	1.00	45.51	A	O
ATOM	2480	CB	PHE	A	322	70.999	30.235	2.321	1.00	49.10	A	C
ATOM	2481	CG	PHE	A	322	69.573	29.925	1.935	1.00	44.63	A	C
ATOM	2482	CD1	PHE	A	322	68.563	29.921	2.894	1.00	45.73	A	C
ATOM	2483	CD2	PHE	A	322	69.248	29.629	0.623	1.00	39.25	A	C
ATOM	2484	CE1	PHE	A	322	67.252	29.634	2.539	1.00	44.70	A	C
ATOM	2485	CE2	PHE	A	322	67.950	29.351	0.261	1.00	41.50	A	C
ATOM	2486	CZ	PHE	A	322	66.947	29.353	1.218	1.00	42.07	A	C
ATOM	2487	N	ALA	A	323	70.339	33.399	1.142	1.00	47.94	A	N
ATOM	2488	CA	ALA	A	323	69.901	34.771	1.336	1.00	46.61	A	C
ATOM	2489	C	ALA	A	323	68.426	34.839	1.712	1.00	44.07	A	C
ATOM	2490	O	ALA	A	323	67.809	35.887	1.548	1.00	33.93	A	O
ATOM	2491	CB	ALA	A	323	70.133	35.564	0.054	1.00	49.38	A	C
ATOM	2492	N	ILE	A	324	67.853	33.725	2.169	1.00	37.73	A	N
ATOM	2493	CA	ILE	A	324	66.520	33.746	2.739	1.00	38.21	A	C
ATOM	2494	C	ILE	A	324	66.643	33.442	4.214	1.00	34.73	A	C
ATOM	2495	O	ILE	A	324	67.442	32.611	4.619	1.00	36.43	A	O
ATOM	2496	CB	ILE	A	324	65.577	32.736	2.038	1.00	38.89	A	C
ATOM	2497	CG1	ILE	A	324	65.714	32.862	0.518	1.00	38.34	A	C
ATOM	2498	CG2	ILE	A	324	64.126	32.960	2.495	1.00	40.76	A	C
ATOM	2499	CD1	ILE	A	324	64.684	32.110	-0.277	1.00	41.65	A	C
ATOM	2500	N	SER	A	325	65.840	34.112	5.020	1.00	32.69	A	N
ATOM	2501	CA	SER	A	325	66.013	34.031	6.460	1.00	38.71	A	C
ATOM	2502	C	SER	A	325	64.722	34.407	7.139	1.00	39.64	A	C
ATOM	2503	O	SER	A	325	63.792	34.883	6.509	1.00	40.29	A	O
ATOM	2504	CB	SER	A	325	67.150	34.953	6.925	1.00	40.03	A	C
ATOM	2505	OG	SER	A	325	66.788	36.327	6.838	1.00	38.81	A	O
ATOM	2506	N	GLN	A	326	64.677	34.221	8.440	1.00	38.99	A	N
ATOM	2507	CA	GLN	A	326	63.414	34.244	9.134	1.00	39.09	A	C
ATOM	2508	C	GLN	A	326	63.294	35.561	9.885	1.00	36.76	A	C
ATOM	2509	O	GLN	A	326	64.259	36.297	10.004	1.00	39.83	A	O
ATOM	2510	CB	GLN	A	326	63.287	33.011	10.037	1.00	41.88	A	C
ATOM	2511	CG	GLN	A	326	64.481	32.024	9.957	1.00	45.10	A	C
ATOM	2512	CD	GLN	A	326	64.374	30.817	10.892	1.00	50.52	A	C
ATOM	2513	OE1	GLN	A	326	65.393	30.286	11.322	1.00	51.97	A	O
ATOM	2514	NE2	GLN	A	326	63.151	30.388	11.202	1.00	51.73	A	N
ATOM	2515	N	SER	A	327	62.108	35.878	10.374	1.00	30.92	A	N
ATOM	2516	CA	SER	A	327	61.904	37.188	10.988	1.00	35.17	A	C
ATOM	2517	C	SER	A	327	60.788	37.140	11.993	1.00	36.09	A	C
ATOM	2518	O	SER	A	327	59.978	36.208	12.018	1.00	38.75	A	O
ATOM	2519	CB	SER	A	327	61.578	38.259	9.921	1.00	35.42	A	C
ATOM	2520	OG	SER	A	327	60.882	39.380	10.482	1.00	33.54	A	O
ATOM	2521	N	SER	A	328	60.723	38.174	12.808	1.00	31.04	A	N
ATOM	2522	CA	SER	A	328	59.597	38.328	13.697	1.00	37.93	A	C
ATOM	2523	C	SER	A	328	58.868	39.654	13.520	1.00	39.07	A	C
ATOM	2524	O	SER	A	328	57.960	39.967	14.296	1.00	43.35	A	O
ATOM	2525	CB	SER	A	328	60.086	38.167	15.123	1.00	41.74	A	C
ATOM	2526	OG	SER	A	328	60.967	39.227	15.485	1.00	45.41	A	O
ATOM	2527	N	THR	A	329	59.257	40.409	12.492	1.00	37.31	A	N
ATOM	2528	CA	THR	A	329	58.675	41.715	12.186	1.00	40.83	A	C
ATOM	2529	C	THR	A	329	58.020	41.703	10.797	1.00	39.53	A	C
ATOM	2530	O	THR	A	329	57.814	42.771	10.218	1.00	37.06	A	O
ATOM	2531	CB	THR	A	329	59.770	42.814	12.193	1.00	42.95	A	C
ATOM	2532	OG1	THR	A	329	60.831	42.455	11.287	1.00	41.26	A	O
ATOM	2533	CG2	THR	A	329	60.441	42.933	13.558	1.00	44.90	A	C
ATOM	2534	N	GLY	A	330	57.724	40.510	10.270	1.00	37.04	A	N
ATOM	2535	CA	GLY	A	330	57.032	40.358	8.988	1.00	35.68	A	C
ATOM	2536	C	GLY	A	330	57.929	39.930	7.836	1.00	34.85	A	C
ATOM	2537	O	GLY	A	330	59.067	39.526	8.047	1.00	32.50	A	O
ATOM	2538	N	THR	A	331	57.398	39.974	6.605	1.00	33.39	A	N

ATOM	2539	CA	THR	A	331	58.207	39.709	5.419	1.00	28.89	A	C
ATOM	2540	C	THR	A	331	58.979	40.971	4.998	1.00	27.79	A	C
ATOM	2541	O	THR	A	331	58.496	42.086	5.175	1.00	33.40	A	O
ATOM	2542	CB	THR	A	331	57.320	39.267	4.249	1.00	30.99	A	C
ATOM	2543	OG1	THR	A	331	56.695	38.020	4.561	1.00	30.88	A	O
ATOM	2544	CG2	THR	A	331	58.157	38.989	2.983	1.00	33.73	A	C
ATOM	2545	N	VAL	A	332	60.177	40.764	4.470	1.00	22.23	A	N
ATOM	2546	CA	VAL	A	332	61.065	41.847	3.989	1.00	27.82	A	C
ATOM	2547	C	VAL	A	332	61.630	41.466	2.632	1.00	24.10	A	C
ATOM	2548	O	VAL	A	332	62.394	40.540	2.501	1.00	26.31	A	O
ATOM	2549	CB	VAL	A	332	62.274	42.139	4.935	1.00	28.52	A	C
ATOM	2550	CG1	VAL	A	332	63.138	43.293	4.367	1.00	32.83	A	C
ATOM	2551	CG2	VAL	A	332	61.801	42.468	6.329	1.00	30.87	A	C
ATOM	2552	N	MET	A	333	61.242	42.199	1.591	1.00	29.37	A	N
ATOM	2553	CA	MET	A	333	61.760	41.968	0.251	1.00	23.35	A	C
ATOM	2554	C	MET	A	333	63.012	42.813	-0.015	1.00	26.09	A	C
ATOM	2555	O	MET	A	333	62.920	43.935	-0.512	1.00	22.66	A	O
ATOM	2556	CB	MET	A	333	60.687	42.296	-0.804	1.00	26.84	A	C
ATOM	2557	CG	MET	A	333	59.550	41.295	-0.855	1.00	28.90	A	C
ATOM	2558	SD	MET	A	333	58.086	41.883	-1.807	1.00	33.93	A	S
ATOM	2559	CE	MET	A	333	58.640	41.701	-3.325	1.00	30.83	A	C
ATOM	2560	N	GLY	A	334	64.179	42.265	0.294	1.00	26.44	A	N
ATOM	2561	CA	GLY	A	334	65.428	43.015	0.190	1.00	28.29	A	C
ATOM	2562	C	GLY	A	334	66.044	43.002	-1.185	1.00	28.85	A	C
ATOM	2563	O	GLY	A	334	65.370	42.791	-2.185	1.00	28.04	A	O
ATOM	2564	N	ALA	A	335	67.350	43.220	-1.243	1.00	29.46	A	N
ATOM	2565	CA	ALA	A	335	68.097	43.214	-2.489	1.00	28.30	A	C
ATOM	2566	C	ALA	A	335	67.939	41.952	-3.330	1.00	31.11	A	C
ATOM	2567	O	ALA	A	335	68.001	42.021	-4.563	1.00	29.82	A	O
ATOM	2568	CB	ALA	A	335	69.578	43.470	-2.206	1.00	34.20	A	C
ATOM	2569	N	VAL	A	336	67.738	40.805	-2.671	1.00	31.66	A	N
ATOM	2570	CA	VAL	A	336	67.506	39.532	-3.349	1.00	35.42	A	C
ATOM	2571	C	VAL	A	336	66.412	39.733	-4.393	1.00	32.46	A	C
ATOM	2572	O	VAL	A	336	66.626	39.464	-5.574	1.00	36.08	A	O
ATOM	2573	CB	VAL	A	336	67.096	38.405	-2.341	1.00	38.14	A	C
ATOM	2574	CG1	VAL	A	336	66.466	37.196	-3.057	1.00	41.63	A	C
ATOM	2575	CG2	VAL	A	336	68.294	37.960	-1.518	1.00	42.38	A	C
ATOM	2576	N	ILE	A	337	65.271	40.248	-3.944	1.00	32.57	A	N
ATOM	2577	CA	ILE	A	337	64.130	40.507	-4.832	1.00	31.81	A	C
ATOM	2578	C	ILE	A	337	64.389	41.687	-5.760	1.00	29.91	A	C
ATOM	2579	O	ILE	A	337	64.231	41.592	-6.969	1.00	27.22	A	O
ATOM	2580	CB	ILE	A	337	62.835	40.731	-4.005	1.00	34.05	A	C
ATOM	2581	CG1	ILE	A	337	62.466	39.472	-3.216	1.00	37.53	A	C
ATOM	2582	CG2	ILE	A	337	61.668	41.174	-4.903	1.00	34.31	A	C
ATOM	2583	CD1	ILE	A	337	61.814	38.383	-4.043	1.00	39.14	A	C
ATOM	2584	N	MET	A	338	64.813	42.816	-5.202	1.00	28.42	A	N
ATOM	2585	CA	MET	A	338	64.909	44.038	-5.998	1.00	27.14	A	C
ATOM	2586	C	MET	A	338	65.914	43.969	-7.154	1.00	28.91	A	C
ATOM	2587	O	MET	A	338	65.753	44.650	-8.166	1.00	28.30	A	O
ATOM	2588	CB	MET	A	338	65.195	45.214	-5.067	1.00	25.93	A	C
ATOM	2589	CG	MET	A	338	64.083	45.457	-4.082	1.00	27.03	A	C
ATOM	2590	SD	MET	A	338	64.367	46.907	-3.076	1.00	25.07	A	S
ATOM	2591	CE	MET	A	338	64.174	48.235	-4.312	1.00	20.81	A	C
ATOM	2592	N	GLU	A	339	66.954	43.142	-7.040	1.00	29.81	A	N
ATOM	2593	CA	GLU	A	339	67.909	43.018	-8.142	1.00	32.30	A	C
ATOM	2594	C	GLU	A	339	67.318	42.371	-9.403	1.00	30.06	A	C
ATOM	2595	O	GLU	A	339	67.874	42.502	-10.488	1.00	33.61	A	O
ATOM	2596	CB	GLU	A	339	69.174	42.269	-7.704	1.00	33.90	A	C
ATOM	2597	CG	GLU	A	339	70.197	43.177	-7.027	1.00	38.40	A	C
ATOM	2598	CD	GLU	A	339	71.139	42.424	-6.107	1.00	42.07	A	C
ATOM	2599	OE1	GLU	A	339	71.439	41.242	-6.391	1.00	39.96	A	O
ATOM	2600	OE2	GLU	A	339	71.570	43.015	-5.095	1.00	43.98	A	O
ATOM	2601	N	GLY	A	340	66.187	41.687	-9.259	1.00	30.73	A	N
ATOM	2602	CA	GLY	A	340	65.475	41.165	-10.411	1.00	29.00	A	C
ATOM	2603	C	GLY	A	340	64.626	42.169	-11.162	1.00	25.72	A	C
ATOM	2604	O	GLY	A	340	64.289	41.949	-12.331	1.00	25.52	A	O
ATOM	2605	N	PHE	A	341	64.278	43.281	-10.509	1.00	21.32	A	N
ATOM	2606	CA	PHE	A	341	63.243	44.173	-11.017	1.00	17.05	A	C
ATOM	2607	C	PHE	A	341	63.561	45.656	-10.971	1.00	19.54	A	C
ATOM	2608	O	PHE	A	341	64.379	46.111	-10.174	1.00	20.37	A	O
ATOM	2609	CB	PHE	A	341	61.961	43.899	-10.222	1.00	18.19	A	C
ATOM	2610	CG	PHE	A	341	61.630	42.440	-10.137	1.00	20.96	A	C
ATOM	2611	CD1	PHE	A	341	61.108	41.770	-11.237	1.00	22.17	A	C
ATOM	2612	CD2	PHE	A	341	61.910	41.717	-8.998	1.00	23.21	A	C
ATOM	2613	CE1	PHE	A	341	60.853	40.399	-11.160	1.00	17.74	A	C
ATOM	2614	CE2	PHE	A	341	61.650	40.351	-8.939	1.00	23.34	A	C
ATOM	2615	CZ	PHE	A	341	61.134	39.705	-10.012	1.00	24.23	A	C

ATOM	2616	N	TYR	A	342	62.952	46.413	-11.875	1.00	17.67	A	N
ATOM	2617	CA	TYR	A	342	62.820	47.837	-11.702	1.00	17.52	A	C
ATOM	2618	C	TYR	A	342	61.608	48.077	-10.810	1.00	22.25	A	C
ATOM	2619	O	TYR	A	342	60.494	47.620	-11.100	1.00	19.30	A	O
ATOM	2620	CB	TYR	A	342	62.656	48.485	-13.040	1.00	17.92	A	C
ATOM	2621	CG	TYR	A	342	62.654	49.980	-13.067	1.00	18.37	A	C
ATOM	2622	CD1	TYR	A	342	63.668	50.730	-12.467	1.00	19.68	A	C
ATOM	2623	CD2	TYR	A	342	61.681	50.654	-13.765	1.00	23.05	A	C
ATOM	2624	CE1	TYR	A	342	63.684	52.115	-12.562	1.00	22.84	A	C
ATOM	2625	CE2	TYR	A	342	61.693	52.006	-13.868	1.00	22.40	A	C
ATOM	2626	CZ	TYR	A	342	62.693	52.750	-13.264	1.00	22.81	A	C
ATOM	2627	OH	TYR	A	342	62.667	54.131	-13.385	1.00	26.20	A	O
ATOM	2628	N	VAL	A	343	61.840	48.777	-9.705	1.00	15.05	A	N
ATOM	2629	CA	VAL	A	343	60.827	49.008	-8.688	1.00	17.53	A	C
ATOM	2630	C	VAL	A	343	60.510	50.494	-8.598	1.00	14.20	A	C
ATOM	2631	O	VAL	A	343	61.378	51.334	-8.376	1.00	15.91	A	O
ATOM	2632	CB	VAL	A	343	61.259	48.442	-7.305	1.00	15.41	A	C
ATOM	2633	CG1	VAL	A	343	60.123	48.560	-6.267	1.00	18.03	A	C
ATOM	2634	CG2	VAL	A	343	61.704	47.022	-7.473	1.00	18.07	A	C
ATOM	2635	N	VAL	A	344	59.231	50.791	-8.767	1.00	11.66	A	N
ATOM	2636	CA	VAL	A	344	58.682	52.123	-8.783	1.00	12.22	A	C
ATOM	2637	C	VAL	A	344	57.903	52.401	-7.510	1.00	13.35	A	C
ATOM	2638	O	VAL	A	344	56.875	51.802	-7.235	1.00	16.24	A	O
ATOM	2639	CB	VAL	A	344	57.774	52.308	-10.027	1.00	15.89	A	C
ATOM	2640	CG1	VAL	A	344	57.159	53.685	-10.035	1.00	18.74	A	C
ATOM	2641	CG2	VAL	A	344	58.587	52.106	-11.280	1.00	18.50	A	C
ATOM	2642	N	PHE	A	345	58.418	53.322	-6.713	1.00	16.40	A	N
ATOM	2643	CA	PHE	A	345	57.771	53.763	-5.483	1.00	15.06	A	C
ATOM	2644	C	PHE	A	345	56.833	54.934	-5.754	1.00	15.39	A	C
ATOM	2645	O	PHE	A	345	57.192	56.113	-5.655	1.00	17.43	A	O
ATOM	2646	CB	PHE	A	345	58.846	54.062	-4.416	1.00	17.40	A	C
ATOM	2647	CG	PHE	A	345	59.670	52.855	-4.040	1.00	15.11	A	C
ATOM	2648	CD1	PHE	A	345	60.702	52.386	-4.863	1.00	13.07	A	C
ATOM	2649	CD2	PHE	A	345	59.402	52.153	-2.882	1.00	13.71	A	C
ATOM	2650	CE1	PHE	A	345	61.446	51.242	-4.510	1.00	15.84	A	C
ATOM	2651	CE2	PHE	A	345	60.169	51.040	-2.507	1.00	11.40	A	C
ATOM	2652	CZ	PHE	A	345	61.186	50.581	-3.327	1.00	15.67	A	C
ATOM	2653	N	ASP	A	346	55.633	54.601	-6.206	1.00	16.44	A	N
ATOM	2654	CA	ASP	A	346	54.671	55.593	-6.672	1.00	15.35	A	C
ATOM	2655	C	ASP	A	346	53.855	56.101	-5.495	1.00	16.03	A	C
ATOM	2656	O	ASP	A	346	52.711	55.700	-5.254	1.00	19.50	A	O
ATOM	2657	CB	ASP	A	346	53.800	54.986	-7.778	1.00	18.03	A	C
ATOM	2658	CG	ASP	A	346	52.872	55.995	-8.420	1.00	25.99	A	C
ATOM	2659	OD1	ASP	A	346	52.844	57.166	-7.967	1.00	28.56	A	O
ATOM	2660	OD2	ASP	A	346	52.120	55.680	-9.382	1.00	23.57	A	O
ATOM	2661	N	ARG	A	347	54.491	56.978	-4.725	1.00	17.55	A	N
ATOM	2662	CA	ARG	A	347	53.908	57.497	-3.499	1.00	21.29	A	C
ATOM	2663	C	ARG	A	347	52.632	58.294	-3.785	1.00	18.95	A	C
ATOM	2664	O	ARG	A	347	51.701	58.266	-2.991	1.00	22.26	A	O
ATOM	2665	CB	ARG	A	347	54.932	58.369	-2.765	1.00	19.24	A	C
ATOM	2666	CG	ARG	A	347	56.184	57.635	-2.282	1.00	22.31	A	C
ATOM	2667	CD	ARG	A	347	57.359	58.594	-2.059	1.00	23.46	A	C
ATOM	2668	NE	ARG	A	347	57.009	59.652	-1.092	1.00	23.99	A	N
ATOM	2669	CZ	ARG	A	347	57.403	59.691	0.183	1.00	30.72	A	C
ATOM	2670	NH1	ARG	A	347	57.031	60.700	0.959	1.00	32.59	A	N
ATOM	2671	NH2	ARG	A	347	58.174	58.745	0.696	1.00	27.96	A	N
ATOM	2672	N	ALA	A	348	52.590	58.959	-4.936	1.00	21.83	A	N
ATOM	2673	CA	ALA	A	348	51.439	59.780	-5.327	1.00	24.64	A	C
ATOM	2674	C	ALA	A	348	50.148	58.953	-5.399	1.00	28.25	A	C
ATOM	2675	O	ALA	A	348	49.056	59.426	-5.028	1.00	24.96	A	O
ATOM	2676	CB	ALA	A	348	51.721	60.425	-6.668	1.00	24.31	A	C
ATOM	2677	N	ARG	A	349	50.282	57.724	-5.896	1.00	25.65	A	N
ATOM	2678	CA	ARG	A	349	49.151	56.806	-6.029	1.00	25.84	A	C
ATOM	2679	C	ARG	A	349	49.168	55.627	-5.077	1.00	25.58	A	C
ATOM	2680	O	ARG	A	349	48.460	54.653	-5.319	1.00	25.28	A	O
ATOM	2681	CB	ARG	A	349	49.100	56.276	-7.459	1.00	29.93	A	C
ATOM	2682	CG	ARG	A	349	49.176	57.344	-8.488	1.00	33.60	A	C
ATOM	2683	CD	ARG	A	349	48.502	57.000	-9.775	1.00	36.74	A	C
ATOM	2684	NE	ARG	A	349	48.827	58.016	-10.763	1.00	42.71	A	N
ATOM	2685	CZ	ARG	A	349	48.278	59.227	-10.814	1.00	48.30	A	C
ATOM	2686	NH1	ARG	A	349	47.316	59.600	-9.964	1.00	46.44	A	N
ATOM	2687	NH2	ARG	A	349	48.686	60.072	-11.751	1.00	50.26	A	N
ATOM	2688	N	LYS	A	350	49.954	55.721	-3.989	1.00	23.32	A	N
ATOM	2689	CA	LYS	A	350	50.022	54.700	-2.945	1.00	24.27	A	C
ATOM	2690	C	LYS	A	350	50.163	53.310	-3.549	1.00	19.69	A	C
ATOM	2691	O	LYS	A	350	49.374	52.429	-3.260	1.00	20.60	A	O
ATOM	2692	CB	LYS	A	350	48.757	54.704	-2.079	1.00	28.78	A	C

ATOM	2693	CG	LYS	A	350	48.522	55.929	-1.231	1.00	34.60	A	C
ATOM	2694	CD	LYS	A	350	47.436	55.639	-0.141	1.00	37.26	A	C
ATOM	2695	CE	LYS	A	350	47.719	54.361	0.695	1.00	36.46	A	C
ATOM	2696	NZ	LYS	A	350	46.822	54.210	1.887	1.00	40.30	A	N
ATOM	2697	N	ARG	A	351	51.147	53.140	-4.420	1.00	19.35	A	N
ATOM	2698	CA	ARG	A	351	51.371	51.855	-5.063	1.00	17.19	A	C
ATOM	2699	C	ARG	A	351	52.842	51.641	-5.383	1.00	15.48	A	C
ATOM	2700	O	ARG	A	351	53.609	52.576	-5.490	1.00	17.66	A	O
ATOM	2701	CB	ARG	A	351	50.501	51.758	-6.328	1.00	15.07	A	C
ATOM	2702	CG	ARG	A	351	50.851	52.687	-7.388	1.00	17.01	A	C
ATOM	2703	CD	ARG	A	351	49.837	52.667	-8.565	1.00	17.81	A	C
ATOM	2704	NE	ARG	A	351	50.304	53.485	-9.674	1.00	17.24	A	N
ATOM	2705	CZ	ARG	A	351	49.711	53.543	-10.862	1.00	23.21	A	C
ATOM	2706	NH1	ARG	A	351	48.651	52.804	-11.095	1.00	21.30	A	N
ATOM	2707	NH2	ARG	A	351	50.213	54.312	-11.831	1.00	24.26	A	N
ATOM	2708	N	ILE	A	352	53.240	50.376	-5.500	1.00	17.16	A	N
ATOM	2709	CA	ILE	A	352	54.581	50.022	-5.928	1.00	16.38	A	C
ATOM	2710	C	ILE	A	352	54.510	49.221	-7.208	1.00	15.28	A	C
ATOM	2711	O	ILE	A	352	53.800	48.234	-7.277	1.00	15.77	A	O
ATOM	2712	CB	ILE	A	352	55.303	49.167	-4.857	1.00	17.10	A	C
ATOM	2713	CG1	ILE	A	352	55.387	49.937	-3.540	1.00	24.67	A	C
ATOM	2714	CG2	ILE	A	352	56.740	48.790	-5.322	1.00	17.46	A	C
ATOM	2715	CD1	ILE	A	352	55.844	49.129	-2.381	1.00	28.46	A	C
ATOM	2716	N	GLY	A	353	55.291	49.633	-8.199	1.00	14.93	A	N
ATOM	2717	CA	GLY	A	353	55.345	48.949	-9.481	1.00	14.98	A	C
ATOM	2718	C	GLY	A	353	56.559	48.090	-9.631	1.00	15.46	A	C
ATOM	2719	O	GLY	A	353	57.649	48.466	-9.185	1.00	14.60	A	O
ATOM	2720	N	PHE	A	354	56.385	46.936	-10.290	1.00	15.06	A	N
ATOM	2721	CA	PHE	A	354	57.469	46.043	-10.577	1.00	14.45	A	C
ATOM	2722	C	PHE	A	354	57.482	45.781	-12.064	1.00	15.57	A	C
ATOM	2723	O	PHE	A	354	56.431	45.590	-12.685	1.00	17.67	A	O
ATOM	2724	CB	PHE	A	354	57.285	44.716	-9.860	1.00	16.68	A	C
ATOM	2725	CG	PHE	A	354	57.443	44.793	-8.362	1.00	16.38	A	C
ATOM	2726	CD1	PHE	A	354	56.371	45.164	-7.563	1.00	16.54	A	C
ATOM	2727	CD2	PHE	A	354	58.640	44.430	-7.756	1.00	19.54	A	C
ATOM	2728	CE1	PHE	A	354	56.490	45.231	-6.177	1.00	20.88	A	C
ATOM	2729	CE2	PHE	A	354	58.771	44.487	-6.362	1.00	19.27	A	C
ATOM	2730	CZ	PHE	A	354	57.684	44.906	-5.571	1.00	15.66	A	C
ATOM	2731	N	ALA	A	355	58.684	45.766	-12.606	1.00	18.28	A	N
ATOM	2732	CA	ALA	A	355	58.922	45.384	-13.999	1.00	16.49	A	C
ATOM	2733	C	ALA	A	355	60.245	44.644	-14.081	1.00	19.90	A	C
ATOM	2734	O	ALA	A	355	61.106	44.777	-13.211	1.00	21.15	A	O
ATOM	2735	CB	ALA	A	355	58.922	46.569	-14.878	1.00	17.48	A	C
ATOM	2736	N	VAL	A	356	60.399	43.827	-15.120	1.00	20.94	A	N
ATOM	2737	CA	VAL	A	356	61.650	43.107	-15.305	1.00	21.72	A	C
ATOM	2738	C	VAL	A	356	62.776	44.111	-15.553	1.00	19.54	A	C
ATOM	2739	O	VAL	A	356	62.672	44.989	-16.402	1.00	21.35	A	O
ATOM	2740	CB	VAL	A	356	61.562	42.087	-16.473	1.00	19.47	A	C
ATOM	2741	CG1	VAL	A	356	62.936	41.435	-16.724	1.00	20.92	A	C
ATOM	2742	CG2	VAL	A	356	60.517	41.025	-16.174	1.00	23.31	A	C
ATOM	2743	N	SER	A	357	63.853	43.982	-14.793	1.00	24.48	A	N
ATOM	2744	CA	SER	A	357	64.963	44.919	-14.883	1.00	26.30	A	C
ATOM	2745	C	SER	A	357	65.767	44.633	-16.142	1.00	26.78	A	C
ATOM	2746	O	SER	A	357	66.071	43.481	-16.420	1.00	30.47	A	O
ATOM	2747	CB	SER	A	357	65.896	44.775	-13.676	1.00	25.63	A	C
ATOM	2748	OG	SER	A	357	67.009	45.645	-13.815	1.00	30.40	A	O
ATOM	2749	N	ALA	A	358	66.128	45.682	-16.867	1.00	32.11	A	N
ATOM	2750	CA	ALA	A	358	67.012	45.567	-18.029	1.00	36.75	A	C
ATOM	2751	C	ALA	A	358	68.445	45.147	-17.666	1.00	38.55	A	C
ATOM	2752	O	ALA	A	358	69.233	44.838	-18.560	1.00	42.49	A	O
ATOM	2753	CB	ALA	A	358	67.025	46.881	-18.802	1.00	37.17	A	C
ATOM	2754	N	CYS	A	359	68.782	45.129	-16.374	1.00	39.61	A	N
ATOM	2755	CA	CYS	A	359	70.124	44.742	-15.920	1.00	41.87	A	C
ATOM	2756	C	CYS	A	359	70.169	43.490	-15.049	1.00	42.74	A	C
ATOM	2757	O	CYS	A	359	71.241	43.132	-14.550	1.00	45.60	A	O
ATOM	2758	CB	CYS	A	359	70.801	45.913	-15.175	1.00	41.64	A	C
ATOM	2759	SG	CYS	A	359	70.275	46.154	-13.447	1.00	42.44	A	S
ATOM	2760	N	HIS	A	360	69.040	42.811	-14.847	1.00	42.50	A	N
ATOM	2761	CA	HIS	A	360	69.071	41.569	-14.081	1.00	43.24	A	C
ATOM	2762	C	HIS	A	360	69.903	40.538	-14.848	1.00	44.08	A	C
ATOM	2763	O	HIS	A	360	69.932	40.545	-16.089	1.00	37.43	A	O
ATOM	2764	CB	HIS	A	360	67.665	41.037	-13.772	1.00	43.88	A	C
ATOM	2765	CG	HIS	A	360	67.018	40.307	-14.909	1.00	42.46	A	C
ATOM	2766	ND1	HIS	A	360	66.587	40.941	-16.054	1.00	43.80	A	N
ATOM	2767	CD2	HIS	A	360	66.711	38.997	-15.067	1.00	43.40	A	C
ATOM	2768	CE1	HIS	A	360	66.053	40.053	-16.876	1.00	42.29	A	C
ATOM	2769	NE2	HIS	A	360	66.107	38.867	-16.295	1.00	40.67	A	N

ATOM	2770	N	VAL	A	361	70.604	39.688	-14.108	1.00	46.31	A	N
ATOM	2771	CA	VAL	A	361	71.444	38.671	-14.736	1.00	53.46	A	C
ATOM	2772	C	VAL	A	361	70.569	37.519	-15.208	1.00	55.15	A	C
ATOM	2773	O	VAL	A	361	69.788	36.965	-14.433	1.00	55.26	A	O
ATOM	2774	CB	VAL	A	361	72.584	38.144	-13.812	1.00	55.33	A	C
ATOM	2775	CG1	VAL	A	361	73.724	39.146	-13.769	1.00	58.02	A	C
ATOM	2776	CG2	VAL	A	361	72.086	37.824	-12.392	1.00	57.18	A	C
ATOM	2777	N	HIS	A	362	70.687	37.191	-16.491	1.00	58.23	A	N
ATOM	2778	CA	HIS	A	362	69.957	36.071	-17.078	1.00	61.27	A	C
ATOM	2779	C	HIS	A	362	70.886	35.268	-17.991	1.00	63.90	A	C
ATOM	2780	O	HIS	A	362	72.106	35.470	-17.978	1.00	63.06	A	O
ATOM	2781	CB	HIS	A	362	68.707	36.570	-17.820	1.00	61.80	A	C
ATOM	2782	CG	HIS	A	362	68.987	37.603	-18.869	1.00	64.30	A	C
ATOM	2783	ND1	HIS	A	362	69.075	38.949	-18.582	1.00	65.54	A	N
ATOM	2784	CD2	HIS	A	362	69.176	37.491	-20.206	1.00	66.55	A	C
ATOM	2785	CE1	HIS	A	362	69.318	39.621	-19.694	1.00	66.26	A	C
ATOM	2786	NE2	HIS	A	362	69.384	38.760	-20.694	1.00	67.04	A	N
ATOM	2787	N	ASP	A	363	70.311	34.348	-18.765	1.00	66.38	A	N
ATOM	2788	CA	ASP	A	363	71.086	33.477	-19.645	1.00	68.15	A	C
ATOM	2789	C	ASP	A	363	70.180	32.971	-20.779	1.00	69.51	A	C
ATOM	2790	O	ASP	A	363	69.558	33.787	-21.466	1.00	68.87	A	O
ATOM	2791	CB	ASP	A	363	71.711	32.343	-18.820	1.00	67.85	A	C
ATOM	2792	CG	ASP	A	363	70.722	31.702	-17.869	1.00	67.03	A	C
ATOM	2793	OD1	ASP	A	363	71.157	31.015	-16.923	1.00	67.42	A	O
ATOM	2794	OD2	ASP	A	363	69.490	31.839	-17.981	1.00	67.25	A	O
ATOM	2795	N	GLU	A	364	70.111	31.651	-20.981	1.00	71.44	A	N
ATOM	2796	CA	GLU	A	364	69.186	31.037	-21.944	1.00	71.30	A	C
ATOM	2797	C	GLU	A	364	68.223	30.026	-21.289	1.00	69.20	A	C
ATOM	2798	O	GLU	A	364	67.280	29.569	-21.938	1.00	70.14	A	O
ATOM	2799	CB	GLU	A	364	69.980	30.351	-23.069	1.00	73.26	A	C
ATOM	2800	CG	GLU	A	364	69.968	31.097	-24.399	1.00	74.89	A	C
ATOM	2801	CD	GLU	A	364	70.651	32.451	-24.320	1.00	76.70	A	C
ATOM	2802	OE1	GLU	A	364	71.868	32.494	-24.028	1.00	77.66	A	O
ATOM	2803	OE2	GLU	A	364	69.969	33.476	-24.549	1.00	79.09	A	O
ATOM	2804	N	PHE	A	365	68.455	29.685	-20.017	1.00	66.67	A	N
ATOM	2805	CA	PHE	A	365	67.630	28.704	-19.299	1.00	64.31	A	C
ATOM	2806	C	PHE	A	365	66.403	29.347	-18.633	1.00	61.08	A	C
ATOM	2807	O	PHE	A	365	65.266	29.082	-19.026	1.00	62.40	A	O
ATOM	2808	CB	PHE	A	365	68.464	27.959	-18.245	1.00	65.86	A	C
ATOM	2809	CG	PHE	A	365	69.365	26.886	-18.819	1.00	67.96	A	C
ATOM	2810	CD1	PHE	A	365	70.557	27.227	-19.461	1.00	68.71	A	C
ATOM	2811	CD2	PHE	A	365	69.029	25.538	-18.705	1.00	68.02	A	C
ATOM	2812	CE1	PHE	A	365	71.395	26.241	-19.989	1.00	68.45	A	C
ATOM	2813	CE2	PHE	A	365	69.860	24.545	-19.232	1.00	68.28	A	C
ATOM	2814	CZ	PHE	A	365	71.045	24.899	-19.874	1.00	68.33	A	C
ATOM	2815	N	ARG	A	366	66.636	30.183	-17.624	1.00	54.06	A	N
ATOM	2816	CA	ARG	A	366	65.544	30.804	-16.874	1.00	49.84	A	C
ATOM	2817	C	ARG	A	366	65.747	32.305	-16.729	1.00	48.18	A	C
ATOM	2818	O	ARG	A	366	66.867	32.816	-16.857	1.00	47.96	A	O
ATOM	2819	CB	ARG	A	366	65.424	30.159	-15.490	1.00	47.56	A	C
ATOM	2820	CG	ARG	A	366	65.240	28.655	-15.525	1.00	43.64	A	C
ATOM	2821	CD	ARG	A	366	64.974	28.012	-14.174	1.00	38.98	A	C
ATOM	2822	NE	ARG	A	366	66.159	27.987	-13.327	1.00	41.26	A	N
ATOM	2823	CZ	ARG	A	366	66.242	27.371	-12.147	1.00	36.86	A	C
ATOM	2824	NH1	ARG	A	366	65.203	26.718	-11.644	1.00	42.11	A	N
ATOM	2825	NH2	ARG	A	366	67.375	27.413	-11.471	1.00	36.33	A	N
ATOM	2826	N	THR	A	367	64.654	33.009	-16.446	1.00	46.71	A	N
ATOM	2827	CA	THR	A	367	64.675	34.468	-16.397	1.00	46.92	A	C
ATOM	2828	C	THR	A	367	63.746	35.043	-15.331	1.00	44.72	A	C
ATOM	2829	O	THR	A	367	62.744	34.435	-14.973	1.00	42.54	A	O
ATOM	2830	CB	THR	A	367	64.306	35.019	-17.783	1.00	46.57	A	C
ATOM	2831	OG1	THR	A	367	65.143	34.406	-18.774	1.00	49.10	A	O
ATOM	2832	CG2	THR	A	367	64.628	36.484	-17.902	1.00	48.33	A	C
ATOM	2833	N	ALA	A	368	64.105	36.219	-14.819	1.00	43.12	A	N
ATOM	2834	CA	ALA	A	368	63.206	36.976	-13.962	1.00	37.88	A	C
ATOM	2835	C	ALA	A	368	61.990	37.417	-14.772	1.00	31.67	A	C
ATOM	2836	O	ALA	A	368	62.091	37.780	-15.946	1.00	33.05	A	O
ATOM	2837	CB	ALA	A	368	63.920	38.185	-13.359	1.00	37.36	A	C
ATOM	2838	N	ALA	A	369	60.827	37.407	-14.133	1.00	30.27	A	N
ATOM	2839	CA	ALA	A	369	59.608	37.776	-14.828	1.00	25.65	A	C
ATOM	2840	C	ALA	A	369	58.590	38.454	-13.917	1.00	18.85	A	C
ATOM	2841	O	ALA	A	369	58.574	38.264	-12.707	1.00	26.84	A	O
ATOM	2842	CB	ALA	A	369	58.988	36.559	-15.484	1.00	26.18	A	C
ATOM	2843	N	VAL	A	370	57.772	39.267	-14.543	1.00	21.79	A	N
ATOM	2844	CA	VAL	A	370	56.623	39.891	-13.921	1.00	22.63	A	C
ATOM	2845	C	VAL	A	370	55.460	39.580	-14.864	1.00	23.34	A	C
ATOM	2846	O	VAL	A	370	55.491	39.970	-16.007	1.00	23.37	A	O

ATOM	2847	CB	VAL	A	370	56.806	41.403	-13.783	1.00	24.21	A	C
ATOM	2848	CG1	VAL	A	370	55.606	42.016	-13.069	1.00	20.64	A	C
ATOM	2849	CG2	VAL	A	370	58.091	41.738	-13.021	1.00	24.95	A	C
ATOM	2850	N	GLU	A	371	54.435	38.890	-14.367	1.00	23.45	A	N
ATOM	2851	CA	GLU	A	371	53.364	38.364	-15.208	1.00	26.07	A	C
ATOM	2852	C	GLU	A	371	52.005	38.601	-14.556	1.00	21.52	A	C
ATOM	2853	O	GLU	A	371	51.886	38.584	-13.346	1.00	22.32	A	O
ATOM	2854	CB	GLU	A	371	53.593	36.859	-15.452	1.00	29.04	A	C
ATOM	2855	CG	GLU	A	371	54.667	36.583	-16.508	1.00	37.79	A	C
ATOM	2856	CD	GLU	A	371	55.383	35.235	-16.373	1.00	42.98	A	C
ATOM	2857	OE1	GLU	A	371	55.957	34.768	-17.389	1.00	47.96	A	O
ATOM	2858	OE2	GLU	A	371	55.428	34.655	-15.271	1.00	46.63	A	O
ATOM	2859	N	GLY	A	372	50.997	38.849	-15.375	1.00	23.24	A	N
ATOM	2860	CA	GLY	A	372	49.629	38.995	-14.902	1.00	20.28	A	C
ATOM	2861	C	GLY	A	372	48.652	39.097	-16.060	1.00	21.84	A	C
ATOM	2862	O	GLY	A	372	49.087	39.076	-17.231	1.00	23.46	A	O
ATOM	2863	N	PRO	A	373	47.355	39.219	-15.790	1.00	20.69	A	N
ATOM	2864	CA	PRO	A	373	46.758	39.117	-14.455	1.00	18.48	A	C
ATOM	2865	C	PRO	A	373	46.427	37.686	-14.050	1.00	19.08	A	C
ATOM	2866	O	PRO	A	373	46.197	36.821	-14.906	1.00	22.98	A	O
ATOM	2867	CB	PRO	A	373	45.466	39.923	-14.607	1.00	20.66	A	C
ATOM	2868	CG	PRO	A	373	45.050	39.692	-16.023	1.00	22.14	A	C
ATOM	2869	CD	PRO	A	373	46.328	39.516	-16.811	1.00	21.78	A	C
ATOM	2870	N	PHE	A	374	46.385	37.445	-12.742	1.00	15.75	A	N
ATOM	2871	CA	PHE	A	374	45.882	36.206	-12.195	1.00	16.86	A	C
ATOM	2872	C	PHE	A	374	44.622	36.442	-11.376	1.00	21.99	A	C
ATOM	2873	O	PHE	A	374	44.370	37.554	-10.943	1.00	19.16	A	O
ATOM	2874	CB	PHE	A	374	46.973	35.539	-11.360	1.00	16.65	A	C
ATOM	2875	CG	PHE	A	374	48.148	35.118	-12.170	1.00	19.99	A	C
ATOM	2876	CD1	PHE	A	374	48.097	33.957	-12.936	1.00	23.38	A	C
ATOM	2877	CD2	PHE	A	374	49.294	35.894	-12.221	1.00	22.80	A	C
ATOM	2878	CE1	PHE	A	374	49.189	33.565	-13.711	1.00	27.21	A	C
ATOM	2879	CE2	PHE	A	374	50.385	35.503	-12.980	1.00	22.14	A	C
ATOM	2880	CZ	PHE	A	374	50.341	34.340	-13.722	1.00	25.11	A	C
ATOM	2881	N	VAL	A	375	43.822	35.392	-11.207	1.00	21.84	A	N
ATOM	2882	CA	VAL	A	375	42.614	35.458	-10.407	1.00	22.25	A	C
ATOM	2883	C	VAL	A	375	42.948	34.876	-9.049	1.00	20.48	A	C
ATOM	2884	O	VAL	A	375	43.281	33.695	-8.943	1.00	24.24	A	O
ATOM	2885	CB	VAL	A	375	41.439	34.656	-11.016	1.00	24.98	A	C
ATOM	2886	CG1	VAL	A	375	40.206	34.758	-10.119	1.00	22.92	A	C
ATOM	2887	CG2	VAL	A	375	41.117	35.152	-12.404	1.00	23.43	A	C
ATOM	2888	N	THR	A	376	42.881	35.710	-8.023	1.00	22.65	A	N
ATOM	2889	CA	THR	A	376	43.104	35.291	-6.637	1.00	22.10	A	C
ATOM	2890	C	THR	A	376	42.027	35.873	-5.737	1.00	17.23	A	C
ATOM	2891	O	THR	A	376	41.856	37.081	-5.647	1.00	20.58	A	O
ATOM	2892	CB	THR	A	376	44.490	35.777	-6.137	1.00	23.66	A	C
ATOM	2893	OG1	THR	A	376	45.515	35.417	-7.080	1.00	25.31	A	O
ATOM	2894	CG2	THR	A	376	44.873	35.046	-4.844	1.00	26.58	A	C
ATOM	2895	N	LEU	A	377	41.265	35.010	-5.080	1.00	22.23	A	N
ATOM	2896	CA	LEU	A	377	40.199	35.472	-4.205	1.00	23.50	A	C
ATOM	2897	C	LEU	A	377	40.708	35.632	-2.776	1.00	27.50	A	C
ATOM	2898	O	LEU	A	377	41.710	35.019	-2.401	1.00	28.12	A	O
ATOM	2899	CB	LEU	A	377	39.046	34.481	-4.217	1.00	26.48	A	C
ATOM	2900	CG	LEU	A	377	38.541	34.109	-5.622	1.00	29.26	A	C
ATOM	2901	CD1	LEU	A	377	37.314	33.287	-5.496	1.00	30.60	A	C
ATOM	2902	CD2	LEU	A	377	38.247	35.344	-6.466	1.00	29.52	A	C
ATOM	2903	N	ASP	A	378	39.981	36.441	-2.014	1.00	29.13	A	N
ATOM	2904	CA	ASP	A	378	40.177	36.631	-0.574	1.00	35.27	A	C
ATOM	2905	C	ASP	A	378	41.540	37.210	-0.251	1.00	33.60	A	C
ATOM	2906	O	ASP	A	378	42.134	36.858	0.760	1.00	36.99	A	O
ATOM	2907	CB	ASP	A	378	40.002	35.325	0.196	1.00	33.08	A	C
ATOM	2908	CG	ASP	A	378	38.627	34.762	0.070	1.00	36.04	A	C
ATOM	2909	OD1	ASP	A	378	37.654	35.549	-0.049	1.00	31.19	A	O
ATOM	2910	OD2	ASP	A	378	38.441	33.532	0.097	1.00	41.39	A	O
ATOM	2911	N	MET	A	379	42.026	38.096	-1.110	1.00	34.47	A	N
ATOM	2912	CA	MET	A	379	43.349	38.682	-0.933	1.00	33.96	A	C
ATOM	2913	C	MET	A	379	43.396	39.613	0.270	1.00	34.59	A	C
ATOM	2914	O	MET	A	379	44.449	39.755	0.871	1.00	37.56	A	O
ATOM	2915	CB	MET	A	379	43.782	39.449	-2.186	1.00	30.92	A	C
ATOM	2916	CG	MET	A	379	44.041	38.562	-3.375	1.00	28.94	A	C
ATOM	2917	SD	MET	A	379	44.749	39.489	-4.761	1.00	26.10	A	S
ATOM	2918	CE	MET	A	379	43.486	40.462	-5.207	1.00	25.48	A	C
ATOM	2919	N	GLU	A	380	42.268	40.233	0.615	1.00	41.66	A	N
ATOM	2920	CA	GLU	A	380	42.182	41.091	1.805	1.00	46.13	A	C
ATOM	2921	C	GLU	A	380	42.498	40.308	3.080	1.00	47.68	A	C
ATOM	2922	O	GLU	A	380	43.208	40.810	3.957	1.00	50.01	A	O
ATOM	2923	CB	GLU	A	380	40.803	41.741	1.927	1.00	48.86	A	C

ATOM	2924	CG	GLU	A	380	40.743	43.189	1.446	1.00	51.99	A	C
ATOM	2925	CD	GLU	A	380	40.851	43.338	-0.066	1.00	55.58	A	C
ATOM	2926	OE1	GLU	A	380	40.498	42.385	-0.799	1.00	56.65	A	O
ATOM	2927	OE2	GLU	A	380	41.282	44.426	-0.524	1.00	57.63	A	O
ATOM	2928	N	ASP	A	381	41.997	39.075	3.169	1.00	46.10	A	N
ATOM	2929	CA	ASP	A	381	42.296	38.192	4.309	1.00	46.90	A	C
ATOM	2930	C	ASP	A	381	43.774	37.804	4.428	1.00	44.71	A	C
ATOM	2931	O	ASP	A	381	44.167	37.175	5.402	1.00	45.68	A	O
ATOM	2932	CB	ASP	A	381	41.448	36.911	4.254	1.00	45.21	A	C
ATOM	2933	CG	ASP	A	381	40.052	37.059	3.994	0.00	50.29	A	C
ATOM	2934	OD1	ASP	A	381	39.485	37.731	4.881	0.00	50.63	A	O
ATOM	2935	OD2	ASP	A	381	39.440	36.553	3.030	0.00	50.70	A	O
ATOM	2936	N	CYS	A	382	44.587	38.137	3.429	1.00	43.03	A	N
ATOM	2937	CA	CYS	A	382	46.026	37.939	3.526	1.00	42.15	A	C
ATOM	2938	C	CYS	A	382	46.693	39.021	4.400	1.00	41.50	A	C
ATOM	2939	O	CYS	A	382	47.808	38.827	4.855	1.00	43.47	A	O
ATOM	2940	CB	CYS	A	382	46.669	37.897	2.137	1.00	41.83	A	C
ATOM	2941	SG	CYS	A	382	45.985	36.643	1.026	1.00	38.22	A	S
ATOM	2942	N	GLY	A	383	45.999	40.133	4.645	1.00	43.76	A	N
ATOM	2943	CA	GLY	A	383	46.521	41.233	5.447	1.00	47.67	A	C
ATOM	2944	C	GLY	A	383	46.200	41.165	6.939	1.00	51.51	A	C
ATOM	2945	O	GLY	A	383	45.034	41.086	7.329	1.00	52.22	A	O
ATOM	2946	N	TYR	A	384	47.239	41.220	7.772	1.00	55.14	A	N
ATOM	2947	CA	TYR	A	384	47.092	41.146	9.227	1.00	57.40	A	C
ATOM	2948	C	TYR	A	384	46.613	42.453	9.878	1.00	58.55	A	C
ATOM	2949	O	TYR	A	384	47.216	43.508	9.687	1.00	56.79	A	O
ATOM	2950	CB	TYR	A	384	48.414	40.719	9.865	1.00	57.72	A	C
ATOM	2951	CG	TYR	A	384	48.357	40.643	11.375	1.00	60.49	A	C
ATOM	2952	CD1	TYR	A	384	47.657	39.623	12.015	1.00	61.73	A	C
ATOM	2953	CD2	TYR	A	384	48.994	41.598	12.167	1.00	62.68	A	C
ATOM	2954	CE1	TYR	A	384	47.597	39.551	13.408	1.00	61.50	A	C
ATOM	2955	CE2	TYR	A	384	48.941	41.536	13.561	1.00	62.87	A	C
ATOM	2956	CZ	TYR	A	384	48.242	40.510	14.173	1.00	62.60	A	C
ATOM	2957	OH	TYR	A	384	48.188	40.443	15.548	1.00	62.41	A	O
ATOM	2958	N	ASN	A	385	45.540	42.359	10.666	1.00	60.14	A	N
ATOM	2959	CA	ASN	A	385	45.049	43.478	11.471	1.00	62.13	A	C
ATOM	2960	C	ASN	A	385	45.450	43.295	12.938	1.00	63.14	A	C
ATOM	2961	1OCT	ASN	A	385	46.043	44.168	13.582	1.00	64.31	A	O
ATOM	2962	CB	ASN	A	385	43.524	43.592	11.362	1.00	62.36	A	C
ATOM	2963	CG	ASN	A	385	43.037	43.666	9.918	1.00	63.95	A	C
ATOM	2964	OD1	ASN	A	385	42.654	42.654	9.326	1.00	64.71	A	O
ATOM	2965	ND2	ASN	A	385	43.043	44.866	9.351	1.00	63.38	A	N
ATOM	2966	2OCT	ASN	A	385	45.193	42.257	13.550	1.00	63.30	A	O
ATOM	2967	O	HOH	W	1	79.629	68.206	12.595	1.00	19.21	W	O
ATOM	2968	O	HOH	W	2	49.015	47.109	-12.447	1.00	16.55	W	O
ATOM	2969	O	HOH	W	3	85.976	52.179	5.603	1.00	21.59	W	O
ATOM	2970	O	HOH	W	4	80.248	66.497	15.419	1.00	25.04	W	O
ATOM	2971	O	HOH	W	5	75.516	59.444	-7.006	1.00	20.45	W	O
ATOM	2972	O	HOH	W	6	64.679	60.731	5.508	1.00	20.67	W	O
ATOM	2973	O	HOH	W	7	52.200	57.481	-0.615	1.00	36.49	W	O
ATOM	2974	O	HOH	W	8	52.125	39.097	-18.355	1.00	30.59	W	O
ATOM	2975	O	HOH	W	9	66.983	62.454	10.671	1.00	21.40	W	O
ATOM	2976	O	HOH	W	10	44.515	33.044	-12.767	1.00	22.53	W	O
ATOM	2977	O	HOH	W	11	80.173	73.603	4.481	1.00	33.04	W	O
ATOM	2978	O	HOH	W	12	47.807	50.724	-13.972	1.00	20.13	W	O
ATOM	2979	O	HOH	W	13	80.860	50.315	0.203	1.00	26.62	W	O
ATOM	2980	O	HOH	W	14	55.473	70.139	-4.604	1.00	53.88	W	O
ATOM	2981	O	HOH	W	15	74.472	71.225	-0.260	1.00	39.12	W	O
ATOM	2982	O	HOH	W	16	40.544	39.218	-3.509	1.00	31.61	W	O
ATOM	2983	O	HOH	W	17	80.450	59.844	12.764	1.00	26.37	W	O
ATOM	2984	O	HOH	W	18	66.075	77.514	3.855	1.00	38.59	W	O
ATOM	2985	O	HOH	W	19	85.138	68.322	12.518	1.00	27.81	W	O
ATOM	2986	O	HOH	W	20	87.998	70.949	7.571	1.00	53.38	W	O
ATOM	2987	O	HOH	W	21	87.495	66.754	13.176	1.00	21.08	W	O
ATOM	2988	O	HOH	W	22	49.756	30.124	-1.047	1.00	45.82	W	O
ATOM	2989	O	HOH	W	23	49.361	33.536	13.751	1.00	66.10	W	O
ATOM	2990	O	HOH	W	24	67.788	54.838	10.862	1.00	28.51	W	O
ATOM	2991	O	HOH	W	25	50.160	45.140	-1.881	1.00	27.20	W	O
ATOM	2992	O	HOH	W	26	82.766	67.175	5.119	1.00	34.54	W	O
ATOM	2993	O	HOH	W	27	45.592	32.973	-7.823	1.00	33.43	W	O
ATOM	2994	O	HOH	W	28	81.090	55.720	18.331	1.00	22.44	W	O
ATOM	2995	O	HOH	W	29	43.057	33.861	0.341	1.00	80.20	W	O
ATOM	2996	O	HOH	W	30	61.780	27.615	13.286	1.00	58.09	W	O
ATOM	2997	O	HOH	W	31	50.466	45.953	8.884	1.00	40.45	W	O
ATOM	2998	O	HOH	W	32	83.327	58.106	0.741	1.00	25.84	W	O
ATOM	2999	O	HOH	W	33	81.327	48.709	18.206	1.00	36.23	W	O
ATOM	3000	O	HOH	W	34	72.944	38.241	4.000	1.00	50.15	W	O

ATOM	3001	O	HOH	W	35	48.453	40.727	-19.960	1.00	41.17	W	O
ATOM	3002	O	HOH	W	36	66.664	48.548	5.951	1.00	33.26	W	O
ATOM	3003	O	HOH	W	37	58.083	43.778	-17.062	1.00	24.83	W	O
ATOM	3004	O	HOH	W	38	55.799	60.814	5.110	1.00	39.72	W	O
ATOM	3005	O	HOH	W	39	79.293	52.119	13.860	1.00	21.39	W	O
ATOM	3006	O	HOH	W	40	77.511	45.900	20.280	1.00	50.24	W	O
ATOM	3007	O	HOH	W	41	50.802	43.439	-20.117	1.00	42.67	W	O
ATOM	3008	O	HOH	W	42	66.106	19.960	-9.172	1.00	47.01	W	O
ATOM	3009	O	HOH	W	43	63.894	58.910	-19.204	1.00	76.51	W	O
ATOM	3010	O	HOH	W	44	76.257	41.684	15.651	1.00	62.92	W	O
ATOM	3011	O	HOH	W	45	54.819	50.279	-18.015	1.00	21.51	W	O
ATOM	3012	O	HOH	W	46	65.401	64.403	6.138	1.00	24.60	W	O
ATOM	3013	O	HOH	W	47	53.853	55.150	-11.636	1.00	29.65	W	O
ATOM	3014	O	HOH	W	48	68.908	67.519	-5.703	1.00	33.79	W	O
ATOM	3015	O	HOH	W	49	79.968	52.673	6.743	1.00	26.80	W	O
ATOM	3016	O	HOH	W	50	48.181	44.979	-10.637	1.00	17.31	W	O
ATOM	3017	O	HOH	W	51	53.488	60.669	-0.029	1.00	31.52	W	O
ATOM	3018	O	HOH	W	52	62.724	61.887	9.306	1.00	24.34	W	O
ATOM	3019	O	HOH	W	53	64.870	59.282	19.837	1.00	40.43	W	O
ATOM	3020	O	HOH	W	54	67.034	55.997	8.478	1.00	18.91	W	O
ATOM	3021	O	HOH	W	55	81.783	69.009	13.884	1.00	24.02	W	O
ATOM	3022	O	HOH	W	56	62.338	60.129	2.848	1.00	20.26	W	O
ATOM	3023	O	HOH	W	57	59.948	49.626	3.509	1.00	20.58	W	O
ATOM	3024	O	HOH	W	58	74.315	61.973	-6.807	1.00	24.90	W	O
ATOM	3025	O	HOH	W	59	72.754	44.483	0.023	1.00	30.57	W	O
ATOM	3026	O	HOH	W	60	85.756	65.674	6.462	1.00	34.66	W	O
ATOM	3027	O	HOH	W	61	65.197	62.897	8.395	1.00	24.15	W	O
ATOM	3028	O	HOH	W	62	83.185	55.955	4.621	1.00	21.13	W	O
ATOM	3029	O	HOH	W	63	68.666	31.435	6.797	1.00	32.75	W	O
ATOM	3030	O	HOH	W	64	70.959	50.115	-0.021	1.00	24.74	W	O
ATOM	3031	O	HOH	W	65	70.634	69.168	18.081	1.00	35.02	W	O
ATOM	3032	O	HOH	W	66	83.133	65.815	2.329	1.00	28.15	W	O
ATOM	3033	O	HOH	W	67	81.369	47.920	15.072	1.00	41.54	W	O
ATOM	3034	O	HOH	W	68	87.299	59.567	9.845	1.00	38.69	W	O
ATOM	3035	O	HOH	W	69	41.854	32.167	-5.319	1.00	34.05	W	O
ATOM	3036	O	HOH	W	70	87.742	64.125	6.529	1.00	68.19	W	O
ATOM	3037	O	HOH	W	71	72.460	68.092	12.019	1.00	27.07	W	O
ATOM	3038	O	HOH	W	72	65.274	42.384	-19.635	1.00	61.51	W	O
ATOM	3039	O	HOH	W	73	85.768	65.313	2.708	1.00	45.28	W	O
ATOM	3040	O	HOH	W	74	62.071	26.325	-12.323	1.00	30.75	W	O
ATOM	3041	O	HOH	W	75	53.548	58.246	7.753	1.00	35.77	W	O
ATOM	3042	O	HOH	W	76	48.415	35.384	-17.283	1.00	49.88	W	O
ATOM	3043	O	HOH	W	77	63.389	66.452	6.071	1.00	24.26	W	O
ATOM	3044	O	HOH	W	78	82.811	58.045	-3.976	1.00	49.01	W	O
ATOM	3045	O	HOH	W	79	73.849	44.456	-1.977	1.00	46.53	W	O
ATOM	3046	O	HOH	W	80	45.102	52.297	-10.384	1.00	27.65	W	O
ATOM	3047	O	HOH	W	81	65.497	47.590	-7.949	1.00	22.50	W	O
ATOM	3048	O	HOH	W	82	60.385	50.571	-20.969	1.00	35.94	W	O
ATOM	3049	O	HOH	W	83	73.977	51.153	-13.532	1.00	42.34	W	O
ATOM	3050	O	HOH	W	84	73.807	75.017	-0.696	1.00	45.17	W	O
ATOM	3051	O	HOH	W	85	89.302	56.875	9.021	1.00	36.01	W	O
ATOM	3052	O	HOH	W	86	59.573	59.896	2.947	1.00	37.55	W	O
ATOM	3053	O	HOH	W	87	69.343	40.980	6.123	1.00	33.99	W	O
ATOM	3054	O	HOH	W	88	52.716	58.960	-10.022	1.00	38.62	W	O
ATOM	3055	O	HOH	W	89	71.368	68.265	20.363	1.00	40.93	W	O
ATOM	3056	O	HOH	W	90	58.025	24.259	10.874	1.00	64.35	W	O
ATOM	3057	O	HOH	W	91	79.324	57.854	-5.249	1.00	28.34	W	O
ATOM	3058	O	HOH	W	92	52.049	42.888	4.777	1.00	33.22	W	O
ATOM	3059	O	HOH	W	93	58.572	51.240	-21.845	1.00	39.18	W	O
ATOM	3060	O	HOH	W	94	58.399	59.801	-15.372	1.00	34.06	W	O
ATOM	3061	O	HOH	W	95	51.199	63.163	-3.700	1.00	34.26	W	O
ATOM	3062	O	HOH	W	96	39.751	42.093	5.333	1.00	63.63	W	O
ATOM	3063	O	HOH	W	97	62.377	69.523	12.319	1.00	37.67	W	O
ATOM	3064	O	HOH	W	98	57.972	57.007	14.799	1.00	35.19	W	O
ATOM	3065	O	HOH	W	99	62.896	33.477	-11.943	1.00	76.49	W	O
ATOM	3066	O	HOH	W	100	77.078	56.466	-5.817	1.00	21.61	W	O
ATOM	3067	O	HOH	W	101	58.723	72.174	10.770	1.00	45.78	W	O
ATOM	3068	O	HOH	W	102	82.563	53.786	6.291	1.00	28.84	W	O
ATOM	3069	O	HOH	W	103	59.353	71.034	3.910	1.00	33.97	W	O
ATOM	3070	O	HOH	W	104	64.748	30.333	-21.491	1.00	39.71	W	O
ATOM	3071	O	HOH	W	105	74.634	59.328	-12.866	1.00	40.33	W	O
ATOM	3072	O	HOH	W	106	55.438	42.543	-19.877	1.00	35.74	W	O
ATOM	3073	O	HOH	W	107	77.532	77.780	-0.830	1.00	47.95	W	O
ATOM	3074	O	HOH	W	108	65.148	68.989	-11.545	1.00	51.49	W	O
ATOM	3075	O	HOH	W	109	57.778	41.274	-18.333	1.00	41.55	W	O
ATOM	3076	O	HOH	W	110	55.086	59.049	16.334	1.00	47.49	W	O
ATOM	3077	O	HOH	W	111	81.228	50.040	13.406	1.00	68.55	W	O

ATOM	3078	O	HOH	W	112	39.213	39.599	-0.284	1.00	54.99	W	O
ATOM	3079	O	HOH	W	113	58.054	38.933	-17.692	1.00	30.12	W	O
ATOM	3080	O	HOH	W	114	46.682	50.824	-7.093	1.00	27.96	W	O
ATOM	3081	O	HOH	W	115	56.111	63.217	-0.389	1.00	31.05	W	O
ATOM	3082	O	HOH	W	116	83.364	67.774	0.538	1.00	32.16	W	O
ATOM	3083	O	HOH	W	117	48.343	27.854	7.458	1.00	45.35	W	O
ATOM	3084	O	HOH	W	118	62.036	71.098	6.922	1.00	37.49	W	O
ATOM	3085	O	HOH	W	119	50.470	55.859	8.484	1.00	50.28	W	O
ATOM	3086	O	HOH	W	120	59.219	48.282	-21.628	1.00	49.61	W	O
ATOM	3087	O	HOH	W	121	70.795	46.171	0.982	1.00	42.89	W	O
ATOM	3088	O	HOH	W	122	67.725	50.769	8.365	1.00	44.67	W	O
ATOM	3089	O	HOH	W	123	62.717	69.639	-10.878	1.00	52.07	W	O
ATOM	3090	O	HOH	W	124	60.253	41.588	-20.165	1.00	31.75	W	O
ATOM	3091	O	HOH	W	125	40.595	48.954	-7.729	1.00	24.22	W	O
ATOM	3092	O	HOH	W	126	60.544	37.484	-18.077	1.00	33.87	W	O
ATOM	3093	O	HOH	W	127	65.662	55.956	21.772	1.00	33.55	W	O
ATOM	3094	O	HOH	W	128	65.944	31.897	-19.969	1.00	51.23	W	O
ATOM	3095	O	HOH	W	129	61.793	76.127	1.749	1.00	56.51	W	O
ATOM	3096	O	HOH	W	130	85.302	59.460	0.012	1.00	36.81	W	O
ATOM	3097	O	HOH	W	131	51.594	64.021	-6.048	1.00	58.01	W	O
ATOM	3098	O	HOH	W	132	54.042	66.667	-6.161	1.00	63.77	W	O
ATOM	3099	O	HOH	W	133	62.332	75.297	4.414	1.00	55.75	W	O
ATOM	3100	O	HOH	W	134	50.042	46.059	-20.292	1.00	73.57	W	O
ATOM	3101	O	HOH	W	135	79.366	53.491	-11.459	1.00	45.91	W	O
ATOM	3102	O	HOH	W	136	62.077	57.368	-20.403	1.00	50.99	W	O
ATOM	3103	O	HOH	W	137	70.534	49.754	8.111	1.00	67.69	W	O
ATOM	3104	O	HOH	W	138	78.803	66.881	19.280	1.00	33.48	W	O
ATOM	3105	O	HOH	W	139	83.041	34.659	-5.519	1.00	42.03	W	O
ATOM	3106	O	HOH	W	140	77.602	56.674	-9.068	1.00	43.32	W	O
ATOM	3107	O	HOH	W	141	80.073	75.620	15.238	1.00	30.64	W	O
ATOM	3108	O	HOH	W	142	80.099	63.907	-8.340	1.00	39.92	W	O
ATOM	3109	O	HOH	W	143	56.033	68.239	-6.044	1.00	52.71	W	O
ATOM	3110	O	HOH	W	144	53.413	63.896	-8.009	1.00	35.96	W	O
ATOM	3111	O	HOH	W	145	89.147	64.107	9.192	1.00	45.54	W	O
ATOM	3112	O	HOH	W	146	37.356	37.399	-3.003	1.00	37.40	W	O
ATOM	3113	O	HOH	W	147	71.841	68.945	-7.695	1.00	67.24	W	O
ATOM	3114	O	HOH	W	148	65.710	25.459	1.815	1.00	68.03	W	O
ATOM	3115	O	HOH	W	149	54.563	32.460	14.878	1.00	45.89	W	O
ATOM	3116	O	HOH	W	150	69.771	32.591	-13.970	1.00	38.39	W	O
ATOM	3117	O	HOH	W	151	40.372	41.672	-3.643	1.00	35.36	W	O
ATOM	3118	O	HOH	W	152	67.233	45.846	-10.950	1.00	26.82	W	O
ATOM	3119	O	HOH	W	153	38.766	47.051	-8.023	1.00	28.56	W	O
ATOM	3120	O	HOH	W	154	81.319	69.504	-2.622	1.00	45.91	W	O
ATOM	3121	O	HOH	W	155	53.761	29.575	-15.833	1.00	38.29	W	O
ATOM	3122	O	HOH	W	156	56.342	73.135	-5.405	1.00	68.20	W	O
ATOM	3123	O	HOH	W	157	53.773	72.306	-0.902	1.00	67.09	W	O
ATOM	3124	O	HOH	W	158	79.692	66.676	-5.072	1.00	50.12	W	O
ATOM	3125	O	HOH	W	159	73.232	38.089	-7.677	1.00	45.17	W	O
ATOM	3126	O	HOH	W	160	46.657	52.288	-3.310	1.00	36.02	W	O
ATOM	3127	O	HOH	W	161	68.327	19.772	-0.212	1.00	70.84	W	O
ATOM	3128	O	HOH	W	162	57.706	29.223	-8.479	1.00	39.36	W	O
ATOM	3129	O	HOH	W	163	80.380	78.795	5.802	1.00	56.31	W	O
ATOM	3130	O	HOH	W	164	56.675	59.728	-19.716	1.00	51.35	W	O
ATOM	3131	O	HOH	W	165	72.021	78.865	10.056	1.00	57.63	W	O
ATOM	3132	O	HOH	W	166	61.187	22.723	11.672	1.00	52.43	W	O
ATOM	3133	O	HOH	W	167	52.637	65.982	-3.596	1.00	43.55	W	O
ATOM	3134	O	HOH	W	168	77.094	59.049	-11.764	1.00	53.68	W	O
ATOM	3135	O	HOH	W	169	82.297	55.117	-5.408	1.00	56.75	W	O
ATOM	3136	O	HOH	W	170	44.896	54.140	-2.621	1.00	44.26	W	O
ATOM	3137	O	HOH	W	171	75.662	48.265	9.068	1.00	31.34	W	O
ATOM	3138	O	HOH	W	172	62.322	26.608	-15.255	1.00	73.50	W	O
ATOM	3139	O	HOH	W	173	70.503	79.530	7.957	1.00	46.42	W	O
ATOM	3140	O	HOH	W	174	78.756	79.738	3.636	1.00	57.59	W	O
ATOM	3141	O	HOH	W	175	63.567	48.079	7.690	1.00	56.49	W	O
ATOM	3142	O	HOH	W	176	73.105	50.182	8.251	1.00	62.98	W	O
ATOM	3143	O	HOH	W	177	74.155	72.309	-2.546	1.00	63.14	W	O
ATOM	3144	O	HOH	W	178	65.269	74.588	10.615	1.00	38.50	W	O
ATOM	3145	O	HOH	W	179	77.404	52.712	-10.561	1.00	40.86	W	O
ATOM	3146	O	HOH	W	180	53.494	69.486	-1.573	1.00	61.27	W	O
ATOM	3147	O	HOH	W	181	44.408	43.630	15.946	1.00	63.55	W	O
ATOM	3148	O	HOH	W	182	45.148	46.355	9.428	1.00	58.76	W	O
ATOM	3149	O	HOH	W	183	78.021	49.570	-0.246	1.00	32.19	W	O
ATOM	3150	O	HOH	W	184	81.804	50.829	-2.607	1.00	38.10	W	O
ATOM	3151	O	HOH	W	185	88.410	73.240	7.564	1.00	56.30	W	O
ATOM	3152	O	HOH	W	186	61.080	66.476	15.948	1.00	68.96	W	O
ATOM	3153	O	HOH	W	187	45.110	31.905	1.445	1.00	67.43	W	O
ATOM	3154	O	HOH	W	188	49.200	55.926	12.964	1.00	72.28	W	O

ATOM	3155	O	HOH	W	189	71.187	76.958	15.269	1.00	39.87	W	O
ATOM	3156	O	HOH	W	190	73.886	47.482	4.081	1.00	53.55	W	O
ATOM	3157	O	HOH	W	191	69.355	68.996	-15.162	1.00	61.52	W	O
ATOM	3158	O	HOH	W	192	82.777	65.787	-8.682	1.00	62.77	W	O
ATOM	3159	O	HOH	W	193	39.736	46.583	7.480	1.00	62.23	W	O
ATOM	3160	O	HOH	W	194	52.055	40.044	-22.266	1.00	55.63	W	O
ATOM	3161	O	HOH	W	195	71.314	50.785	-16.556	1.00	49.70	W	O
ATOM	3162	O	HOH	W	196	61.950	38.755	-19.713	1.00	70.81	W	O
ATOM	3163	O	HOH	W	197	84.051	69.275	5.460	1.00	48.64	W	O
ATOM	3164	O	HOH	W	198	76.032	60.681	20.880	1.00	69.12	W	O
ATOM	3165	O	HOH	W	199	73.266	44.918	4.326	1.00	68.75	W	O
ATOM	3166	O	HOH	W	200	82.129	50.468	-5.451	1.00	59.02	W	O
ATOM	3167	O	HOH	W	201	83.221	72.917	3.600	1.00	40.04	W	O
ATOM	3168	O	HOH	W	202	59.652	75.257	4.275	1.00	57.30	W	O
ATOM	3169	O	HOH	W	203	78.123	47.635	22.706	1.00	45.73	W	O
ATOM	3170	O	HOH	W	204	77.637	76.375	11.568	1.00	43.51	W	O
ATOM	3171	O	HOH	W	205	58.555	48.938	13.305	1.00	48.92	W	O
ATOM	3172	O	HOH	W	206	57.638	66.927	18.153	1.00	50.79	W	O
ATOM	3173	O	HOH	W	207	58.312	43.498	7.697	1.00	33.77	W	O
ATOM	3174	O	HOH	W	208	44.538	28.297	3.536	1.00	55.65	W	O
ATOM	3175	O	HOH	W	209	59.595	53.833	19.308	1.00	58.04	W	O
ATOM	3176	O	HOH	W	210	57.084	51.317	14.707	1.00	51.78	W	O
ATOM	3177	O	HOH	W	211	49.436	21.830	-1.938	1.00	62.41	W	O
ATOM	3178	O	HOH	W	212	60.734	77.657	4.018	1.00	73.34	W	O
ATOM	3179	O	HOH	W	213	79.123	83.308	3.898	1.00	63.20	W	O
ATOM	3180	O	HOH	W	214	57.523	61.921	-13.519	1.00	37.25	W	O
ATOM	3181	O	HOH	W	215	71.168	43.072	5.167	1.00	41.82	W	O
ATOM	3182	O	HOH	W	216	76.653	84.242	3.301	1.00	78.23	W	O
ATOM	3183	O	HOH	W	217	42.382	40.135	17.622	1.00	61.51	W	O
ATOM	3184	O	HOH	W	218	78.733	69.517	-5.343	1.00	61.81	W	O
ATOM	3185	O	HOH	W	219	62.986	22.749	-4.555	1.00	42.82	W	O
ATOM	3186	O	HOH	W	220	60.743	44.247	9.220	1.00	48.58	W	O
ATOM	3187	O	HOH	W	221	57.413	29.275	-13.554	1.00	41.77	W	O
ATOM	3188	O	HOH	W	222	71.784	39.808	-3.358	1.00	49.72	W	O
ATOM	3189	O	HOH	W	223	74.571	63.700	-13.618	1.00	53.93	W	O
ATOM	3190	O	HOH	W	224	71.261	51.431	-13.741	1.00	41.48	W	O
ATOM	3191	O	HOH	W	225	78.559	79.217	0.998	1.00	50.39	W	O
ATOM	3192	O	HOH	W	226	68.431	42.241	17.534	1.00	51.33	W	O
ATOM	3193	O	HOH	W	227	74.858	56.378	23.475	1.00	62.51	W	O
ATOM	3194	O	HOH	W	228	79.307	60.745	22.219	1.00	40.98	W	O
ATOM	3195	O	HOH	W	229	60.314	68.573	10.249	1.00	29.74	W	O
ATOM	3196	O	HOH	W	230	61.602	71.621	-9.518	1.00	51.81	W	O
ATOM	3197	O	HOH	W	231	49.899	42.585	7.057	1.00	35.46	W	O
ATOM	3198	O	HOH	W	232	46.590	57.769	2.535	1.00	69.32	W	O
ATOM	3199	O	HOH	W	233	45.044	34.173	-1.541	1.00	50.34	W	O
ATOM	3200	O	HOH	W	234	71.447	46.668	-18.182	1.00	58.66	W	O
ATOM	3201	O	HOH	W	235	73.000	43.214	-18.003	1.00	45.06	W	O
ATOM	3202	O	HOH	W	236	43.370	55.663	-1.011	1.00	61.60	W	O
ATOM	3203	O	HOH	W	237	74.007	57.458	-17.330	1.00	59.05	W	O
ATOM	3204	O	HOH	W	238	78.277	52.906	-16.612	1.00	65.63	W	O
ATOM	3205	O	HOH	W	239	77.796	59.191	-8.755	1.00	45.94	W	O
ATOM	3206	O	HOH	W	240	84.436	60.164	-3.135	1.00	53.03	W	O
ATOM	3207	O	HOH	W	241	65.112	49.259	9.447	1.00	53.21	W	O
ATOM	3208	O	HOH	W	242	63.207	51.425	10.118	1.00	42.58	W	O
ATOM	3209	O	HOH	W	243	89.242	51.621	10.559	1.00	37.79	W	O
ATOM	3210	O	HOH	W	244	88.861	58.033	-1.500	1.00	63.56	W	O
ATOM	3211	O	HOH	W	245	80.840	77.800	12.517	1.00	43.88	W	O
ATOM	3212	O	HOH	W	246	77.216	83.653	0.754	1.00	66.92	W	O
ATOM	3213	O	HOH	W	247	69.579	67.222	23.238	1.00	67.75	W	O
ATOM	3214	O	HOH	W	248	75.887	51.320	21.816	1.00	72.66	W	O
ATOM	3215	O	HOH	W	249	68.191	78.916	4.291	1.00	52.82	W	O
ATOM	3216	O	HOH	W	250	82.004	63.181	21.579	1.00	30.60	W	O
ATOM	3217	O	HOH	W	251	76.390	67.886	21.910	1.00	51.17	W	O
ATOM	3218	O	HOH	W	252	53.503	60.921	17.416	1.00	72.58	W	O
ATOM	3219	O	HOH	W	253	60.509	46.370	-23.693	1.00	62.40	W	O
ATOM	3220	O	HOH	W	254	53.842	41.622	-18.205	1.00	43.31	W	O
ATOM	3221	O	HOH	W	255	48.037	45.876	-0.170	1.00	42.34	W	O
ATOM	3222	O	HOH	W	256	44.592	45.050	2.573	1.00	46.37	W	O
ATOM	3223	O	HOH	W	257	40.130	44.608	4.624	1.00	61.11	W	O
ATOM	3224	O	HOH	W	258	69.355	47.143	5.898	1.00	60.82	W	O
ATOM	3225	O	HOH	W	259	34.957	32.570	1.397	1.00	47.77	W	O
ATOM	3226	O	HOH	W	260	61.555	31.492	-14.640	1.00	63.05	W	O
ATOM	3227	O	HOH	W	261	43.862	53.451	-5.566	1.00	71.67	W	O
ATOM	3228	O	HOH	W	262	84.234	48.309	0.364	1.00	54.03	W	O
ATOM	3229	O	HOH	W	263	87.932	51.816	-3.215	1.00	57.80	W	O
ATOM	3230	O	HOH	W	264	82.425	63.456	-6.283	1.00	62.42	W	O
ATOM	3231	O	HOH	W	265	80.271	28.172	9.463	1.00	40.70	W	O

ATOM	3232	O	HOH	W	266	73.963	30.020	4.302	1.00	26.30	W	O
ATOM	3233	O	HOH	W	267	83.112	71.680	1.066	1.00	51.04	W	O
ATOM	3234	O	HOH	W	268	63.047	54.124	10.355	1.00	50.34	W	O
ATOM	3235	O	HOH	W	269	83.682	62.329	-4.165	1.00	42.75	W	O
ATOM	3236	O	HOH	W	270	61.547	73.522	-7.931	1.00	47.36	W	O
ATOM	3237	O	HOH	W	271	60.577	53.517	13.966	1.00	53.55	W	O
ATOM	3238	O	HOH	W	272	54.580	71.014	-6.905	1.00	46.69	W	O
ATOM	3239	O	HOH	W	273	77.926	39.031	-0.508	1.00	49.59	W	O
ATOM	3240	O	HOH	W	274	69.669	49.137	-17.891	1.00	45.33	W	O
ATOM	3241	O	HOH	W	275	44.777	49.840	1.964	1.00	44.62	W	O
ATOM	3242	O	HOH	W	276	48.453	54.600	5.308	1.00	39.43	W	O
ATOM	3243	O	HOH	W	277	51.764	32.262	13.155	1.00	71.42	W	O
ATOM	3244	O	HOH	W	278	60.951	29.296	11.161	1.00	53.99	W	O
ATOM	3245	O	HOH	W	279	68.206	23.452	8.777	1.00	50.70	W	O
ATOM	3246	O	HOH	W	280	87.567	24.412	-10.981	1.00	49.42	W	O
ATOM	3247	O	HOH	W	281	81.650	24.690	-15.233	1.00	46.79	W	O
ATOM	3248	O	HOH	W	282	83.121	29.023	-15.678	1.00	59.22	W	O
ATOM	3249	O	HOH	W	283	81.854	31.654	-13.384	1.00	44.68	W	O
ATOM	3250	O	HOH	W	284	43.424	43.922	-5.261	1.00	38.18	W	O
ATOM	3251	O	HOH	W	285	80.484	32.987	-6.395	1.00	39.87	W	O
ATOM	3252	I	IOD	J	1	80.243	57.842	15.501	0.75	23.63	J	I
ATOM	3253	I	IOD	J	2	81.546	50.334	15.785	0.50	35.87	J	I
ATOM	3254	I	IOD	J	3	51.528	57.888	-13.233	0.50	56.82	J	I

END

CLAIMS

1. A BACE protein, which comprises the sequence set out in residues 45 to 455 of SEQ ID NO:2 (43 to 453 SwissProt P56817), or a fragment thereof comprising residues corresponding to 58 to 398 of SEQ ID NO:2, modified by the following changes:

   (a) substitution or deletion of at least one residue which is a proteolytic cleavage site recognised by clostripain; and optionally

   (b) the replacement of from 1 to 30 other amino acids by an equivalent or fewer number of amino acids.

2. A protein according to claim 1 wherein at least one of residues 44, 47, 57, 58 and 59 of SEQ ID NO:2 are substituted.

3. A protein according to claim 1 or 2 wherein residues 58 and/or 59 are lysine.

4. A protein according to any one of the preceding claims wherein the asparagine residues at positions 155, 174, 225 and 356 (SwissProt P56817 153, 172, 223 and 354) are replaced by glutamine residues.

5. A protein according to any one of the preceding claims wherein the fragment is truncated at the C-terminus such that at least residues 449 *et seq.* of SEQ ID NO:2 are absent.

6. A method of making a truncated BACE protein, which method comprises proteolytically cleaving the protein of any one of the preceding claims.

7. The method of claim 6 wherein said cleavage is at and including one or more of residues 44, 47, 57, 58 and 59.

8. A BACE protein obtained or obtainable by the method of claim 7.

9. A protein according to claim 8 wherein the N-terminal is residue 45 of SEQ ID NO:2.

10. A protein according to claim 1 which is selected from: (a) SEQ ID 6; (b) SEQ ID 8; (c) SEQ ID 10; (d) SEQ ID 12; (e) SEQ ID 14; (f) SEQ ID 16; (g) SEQ ID 18; or a

protein according to claim 7 which is selected from (h) SEQ ID 19; (i) SEQ ID 20; (j) SEQ ID 21.

11. Nucleic acid encoding the protein of any one of claims 1 to 5 or 8 to 10.

12. A vector comprising the nucleic acid of claim 11.

13. A host cell comprising the vector of claim 12.

14. A process for producing the protein of any one of claims 1 to 5 or 8 to 10 comprising the steps of: (a) culturing the host cell of claim 13 under conditions suitable for expression of the protein; and optionally (b) isolating the expressed recombinant BACE protein.

15. A process for producing refolded recombinant BACE protein comprising the steps of: (a) solubilising the recombinant BACE; (b) diluting the solubilised BACE into an aqueous buffer containing 10 to 50 mM sulfobetaine; and (c) maintaining the diluted solution at low temperature and at high pH for at least 2 weeks.

16. A process for producing a crystal of BACE comprising the step of refolding recombinant BACE protein according to the process of claim 14.

17. A process for producing a crystal of a BACE protein comprising the step of growing the crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME, 180-220 mM ammonium iodide and 180-220 mM tri-sodium citrate pH 6.4-6.6, and optionally 0-5% glycerol.

18. A process according to any one of claims 15 to 17 wherein the BACE protein is human BACE.

19. A process according to any one of claims 15 to 17 wherein the BACE protein is as defined in any one of claims 1 to 5 or 8 to 10.

20. A crystal of a BACE protein having a hexagonal space group $P6_122$.

21. The crystal of claim 20 having unit cell dimensions of a=b=103.2 Å, c=169.1 Å, $\alpha=\beta=60°$, $\gamma=120°$, and a unit cell variability of 5% in all dimensions.

22. A crystal of a BACE protein comprising a structure defined by all or a portion of the co-ordinates of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å.

23. A crystal of the protein of any one of claims 1 to 5 or 8 to 10.

24. The crystal of any one of claims 20 to 23 having a resolution better than 2.5 Å.

25. The crystal of any one of claims 20 to 24 which is soaked with one or more compound(s) to form co-complex structures.

26. The crystal of any one of claims 20 to 24 wherein the BACE is co-crystallized with one or more compound(s) to form co-crystallized structures.

27. The crystal of any one of claims 20 to 24 which is an apo crystal.

28. A computer-based method for the analysis of the interaction of a molecular structure with a BACE protein, which comprises:

(a) providing a structure comprising a three-dimensional representation of BACE or of a portion of BACE, which representation comprises all or a portion of the coordinates of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å;

(b) providing a molecular structure to be fitted to said BACE structure; and

(c) fitting the molecular structure to the BACE structure of (a).

29. The method of claim 28 wherein the molecular structure to be fitted is in the form of a model of a pharmacophore.

30. The method of claim 28 or 29 wherein the three-dimensional representation is a model constructed from all or a portion of the coordinates of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å.

31. The method of claim 30 wherein the model is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

32. A computer-based method for the analysis of molecular structures which comprises:

(a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å ("selected coordinates");

(b) providing the structure of a molecular structure to be fitted to the selected coordinates; and

(c) fitting the structure to the selected coordinates of the BACE structure.

33. The method of claim 32 wherein the selected coordinates are of at least 5, 10, 50, 100 or 500 atoms.

34. The method of any one of claims 28 to 33 wherein the coordinates of Table 1 represent a binding pocket.

35. The method of claim 34 wherein the coordinates of Table 1 comprise those relating to residues SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368 (based on the numbering of SwissProt P56817).

36. A computer-based method of rational drug design comprising the method of any one of claims 28 to 35.

37. A computer-based method of rational drug design comprising comprising:

(a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å ("selected coordinates");

(b) providing the structures of a plurality of molecular fragments;

(c) fitting the structure of each of the molecular fragments to the selected coordinates; and

(d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

38. A method for identifying a candidate modulator of BACE comprising the steps of:

(a) employing a three-dimensional structure of BACE, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one BACE binding cavity, the three-dimensional structure being defined by atomic coordinate data according to Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å; and

(b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

39. The method of any one of claims 28 to 38 further comprising the step of:

(a) obtaining or synthesising the molecular structure or modulator; and

(b) contacting the molecular structure or modulator with BACE to determine the ability of the molecular structure or modulator to interact with BACE.

40. A method of assessing the ability of a candidate modulator to interact with BACE which comprises the steps of:

(a) obtaining or synthesising said candidate modulator;

(b) forming a crystallized complex of a BACE protein of claims 1 to 5 or 8 to 10 and said candidate modulator; and

(c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said candidate modulator to interact with BACE.

41. A method for determining the structure of a compound bound to BACE, said method comprising:

(a) mixing BACE with the compound to form a BACE-compound complex;

(b) crystallizing the BACE-compound complex; and

(c) determining the structure of said BACE-compound(s) complex by reference to the data of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å.

42. A method for determining the structure of a compound bound to BACE, said method comprising:

(a) providing a crystal of BACE;

(b) soaking the crystal with one or more compound(s) to form a complex; and

(c) determining the structure of the complex by employing the data of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å.

43. A method of determining the three dimensional structure of a BACE homologue or analogue of unknown structure, the method comprising the steps of:

(a) aligning a representation of an amino acid sequence of the BACE homologue or analogue with the amino acid sequence of the BACE of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å to match homologous regions of the amino acid sequences;

(b) modelling the structure of the matched homologous regions of said target BACE of unknown structure on the corresponding regions of the BACE structure as defined by Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å; and

(c) determining a conformation for the BACE homologue or analogue which substantially preserves the structure of said matched homologous regions.

44. A method of providing data for generating structures and/or performing rational drug design for BACE, BACE homologues or analogues, complexes of BACE with a potential modulator, or complexes of BACE homologues or analogues with potential modulators, the method comprising (i) establishing communication with a remote device containing computer-readable data comprising at least one of:

(a) atomic coordinate data according to Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å, said data defining the three-dimensional

structure of BACE, at least one sub-domain of the three-dimensional structure of BACE, or the coordinates of a plurality of atoms of BACE;

(b) structure factor data for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(c) atomic coordinate data of a target BACE homologue or analogue generated by homology modelling of the target based on the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; and

(e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(ii) receiving said computer-readable data from said remote device.

45. A computer system containing one or more of:

(a) atomic coordinate data according to Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å, said data defining the three-dimensional structure of BACE or at least selected coordinates thereof;

(b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(d) atomic coordinate data of a target BACE protein generated by interpreting X ray crystallographic data or NMR data by reference to the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; or

(e) structure factor data derivable from the atomic coordinate data of (c) or (d).

46. The computer system of claim 45 comprising: a computer-readable data storage medium comprising data storage material encoded with the computer-readable data;

(a) a working memory for storing instructions for processing said computer-readable data; and

(b) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-readable data and thereby generating structures and/or performing rational drug design.

47. A method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1 $\pm$ a root mean square deviation from the $C\alpha$ atoms of less than 0.5Å, and either

(a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or

(b) assigning NMR spectra Peaks of said protein by manipulating the coordinates of Table 1 $\pm$ a root mean square deviation from the $C\alpha$ atoms of less than 0.5Å.

48. A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of any one of claims 28 to 40, and admixing the molecule with a carrier.

49. A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined in any one of claims 28 to 40; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

50. A process according to claim 49 which comprises (a) identifying a molecular structure or modulator according to the method as defined in any one of claims 28 to 40; (b) optimising the structure of the modulator molecule; and (c) preparing a

medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

51. A compound identified, produced or obtainable by the process or method of any one of claims 28 to 40.

52. A compound of claim 51 or composition thereof for use in medicine.

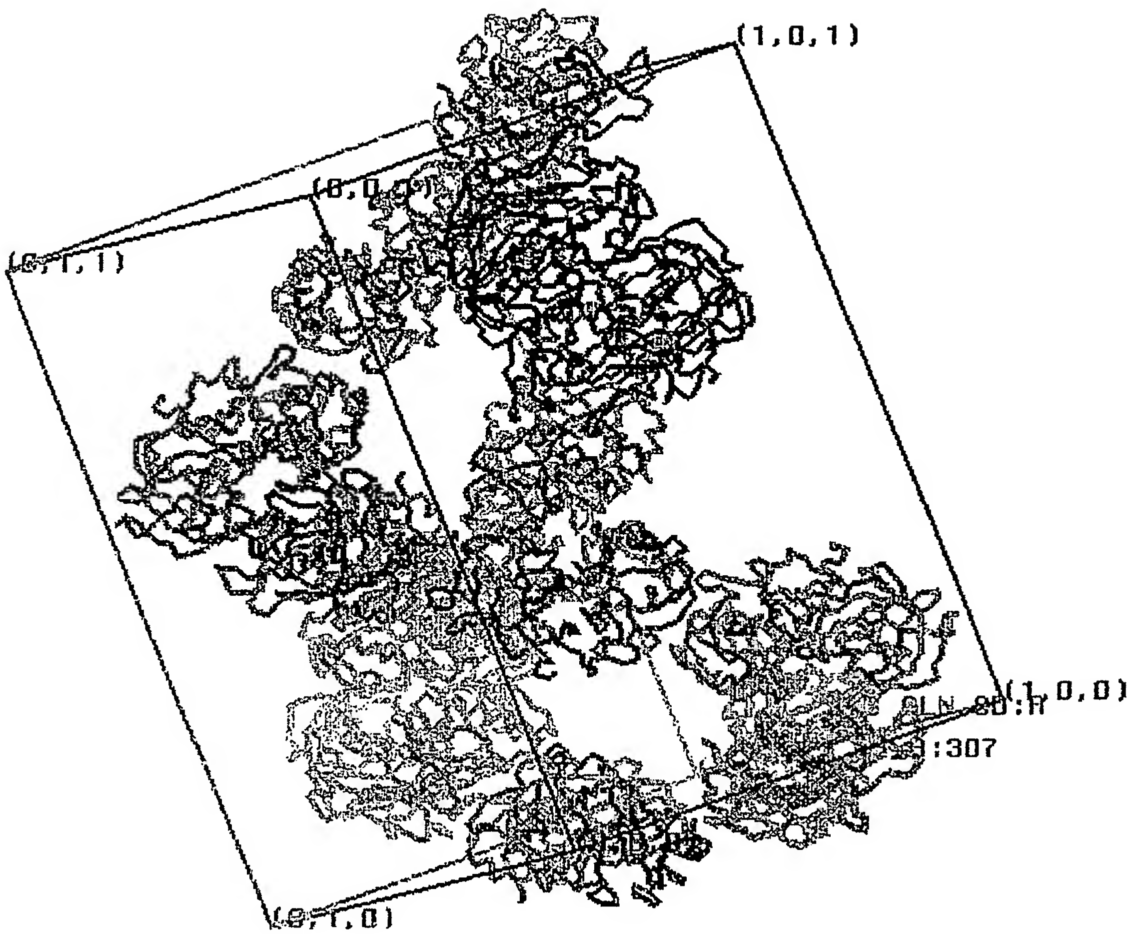

FIGURE 1

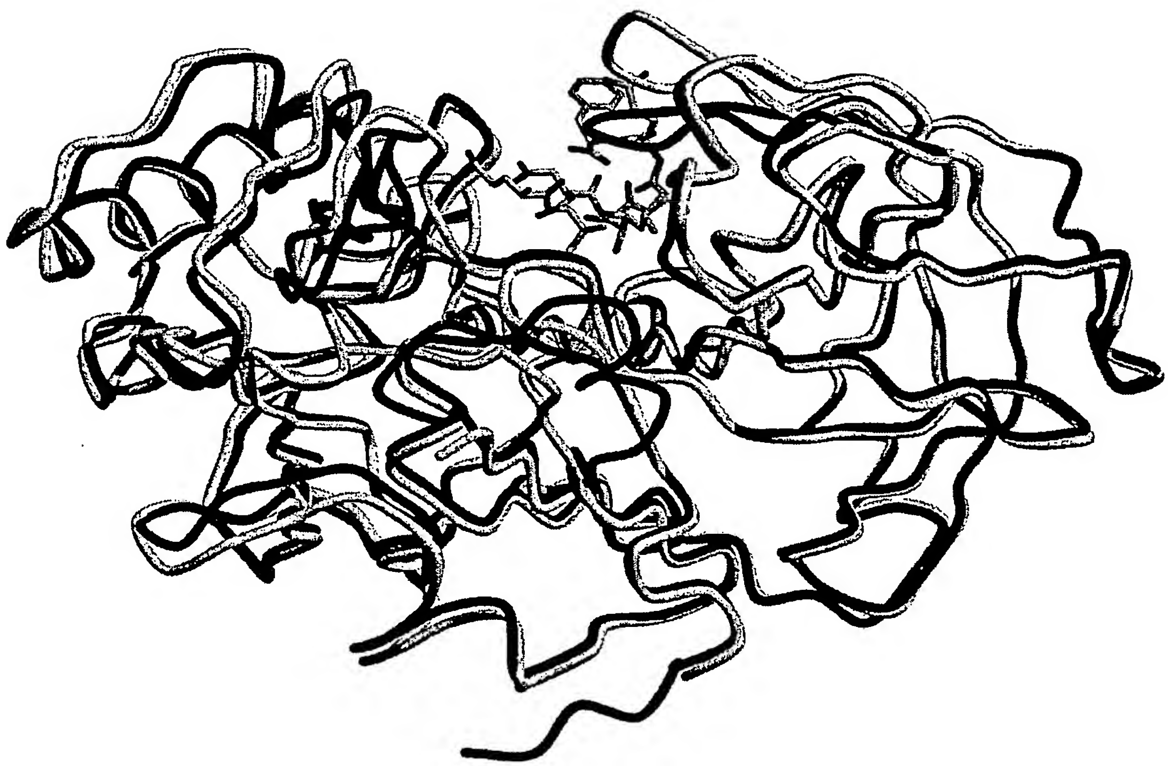

FIGURE 2

Sequence Listings

SEQ ID 1: shows the DNA sequence coding for the BACE protein, BACE WT.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA

SEQ ID 2: shows the deduced amino acid sequence for BACE WT.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRRGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES

SEQ ID 3: shows the DNA sequence coding for the BACE protein, BACE N->Q.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC

ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA

SEQ ID 4: shows the deduced amino acid sequence for BACE N->Q.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRRGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH

SEQ ID 5: shows the DNA sequence coding for the BACE WT R56KR57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA

SEQ ID 6: shows the deduced amino acid sequence for BACE WT R56KR57K

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES

SEQ ID 7: shows the DNA sequence coding for the BACE WT R57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAAGGGC

AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA

SEQ ID 8: shows the deduced amino acid sequence for BACE WT R57K.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES

SEQ ID 9: shows the DNA sequence coding for the BACE WT R57DEL.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAGGGGCAGC
TTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATG
ACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTTT
GCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGC
ACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAAGGG
GAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAACGTCACTGTGCGTGCCAAC
ATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCAACGGCTCCAACTGGGAAGGCATC
CTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGAC
TCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGGC
TTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGAGGT
ATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGGTAT
TATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGCAAG
GAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCCAAG
AAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCT
GATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAAC
ATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCCGCATC
ACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGACGAC
TGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATG
GAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGCGCT
TGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTGGAC
ATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAA

SEQ ID 10: shows the deduced amino acid sequence for BACE WT R57del.

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRGSFVEMVDNLRGKSGQ
GYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLVS
IPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRITILPQQYLRP
VEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDES

SEQ ID 11: shows the DNA sequence coding for the BACE N->Q R56KR57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA

SEQ ID 12: shows the deduced amino acid sequence for BACE N->Q R56KR57K

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH

SEQ ID 13: shows the DNA sequence coding for the BACE N->Q R56KR57K no His.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCAAGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC

ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCATAG

SEQ ID 14: shows the deduced amino acid sequence for BACE N->Q R56KR57K no His

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGKKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR
PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDES

SEQ ID 15: shows the DNA sequence coding for the BACE N->Q R57K.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCT
GCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCC
CTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCGAGGAGCCCGGCCGGAAGGGC
AGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAG
ATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAAC
TTTGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCC
AGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGAA
GGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCC
AACATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGC
ATCCTGGGGCTGGCCTATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTT
GACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCT
GGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGA
GGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGG
TATTATGAGGTGATCATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGC
AAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCC
AAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTC
CCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGG
AACATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGC
ATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGCCACGTCCCAAGAC
GACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATC
ATGGAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGC
GCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTG
GACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGTCACATCACCATCATCAC
CACTAA

SEQ ID 16: shows the deduced amino acid sequence for BACE N->Q R57K

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRKGSFVEMVDNLRGKSG
QGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLV
SIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGF
PLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN
LRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLR

PVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMED
CGYNIPQTDESHHHHHH

SEQ ID 17: shows the DNA sequence coding for the BACE N->Q R57DEL.

ATGGCTAGCATGACTGGTGGACAGCAAATGGGTCGCGGATCCATGGCGGGAGTGCTGCCTGCCCACGGCACCCAGCACGG
CATCCGGCTGCCCCTGCGCAGCGGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAGCCCG
AGGAGCCCGGCAGGGGCAGCTTTGTGGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATG
ACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTTTGCAGTGGGTGCTGCCCCCCA
CCCCTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACA
CCCAGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCCAGGTCACTGTGCGTGCCAAC
ATTGCTGCCATCACTGAATCAGACAAGTTCTTCATCCAGGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCTATGCTGA
GATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCTCTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCC
TGCAGCTTTGTGGTGCTGGCTTCCCCCTCCAGCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGATCATTGGAGGT
ATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCCATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCG
GGTGGAGATCAATGGACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCA
CCAACCTTCGTTTGCCCAAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCT
GATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAACATTTTCCCAGTCATCTCACT
CTACCTAATGGGTGAGGTTACCCAGCAGTCCTTCCGCATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATG
TGGCCACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATG
GAGGGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGCCATGTGCACGATGAGTT
CAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACAGATGAGT
CACATCACCATCATCACCACTAA

SEQ ID 18: shows the deduced amino acid sequence for BACE N->Q R57del

MASMTGGQQMGRGSMAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRGSFVEMVDNLRGKSGQ
GYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLVS
IPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNL
RLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTQQSFRITILPQQYLRP
VEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESHHHHHH

SEQ ID 19: shows the amino acid sequence of BACE WT R56KR57K crystallised.

LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTNQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDES

SEQ ID 20: shows the amino acid sequence of BACE N->Q R56KR57K no His as crystallised.

LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTQQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDES

SEQ ID 21: shows the amino acid sequence of BACE N->Q R56KR57K crystallised.

LPRETDEEPEEPGKKGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQ
LSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPQVTVRANIAAITESDKFFIQGSNWEGILGLAYAEIARP
DDSLEPFFDSLVKQTHVPNLFSLQLCGAGFPLQQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVII
VRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPW
NIFPVISLYLMGEVTQQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKR
IGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESHHHHHH